STIC SEARCH


```
=> b hcaplus
FILE 'HCAPLUS' ENTERED AT 12:26:51 ON 06 NOV 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 6 Nov 2002  VOL 137 ISS 19
FILE LAST UPDATED: 5 Nov 2002  (20021105/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

CAS roles have been modified effective December 16, 2001. Please
check your SDI profiles to see if they need to be revised. For
information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.

=> d que l7
L1          738 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LEUKOTRIENE ANTAGONISTS+OLD/CT

L2          266 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "LEUKOTRIENE RECEPTORS (L)
                LEUKOTRIENE B4"+OLD/CT
L3         4657 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LEUKOTRIENE B4/CT
L4         1081 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((L2 OR L3)(L)(ANTAG? OR
                INHIB?)) OR (L1 AND (L2 OR L3))
L5         1618 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "CYCLOOXYGENASE 2"/CT
L6          650 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5(L)(INHIB? OR ANTAG?)
L7           15 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 AND L6


=> d que l60
L1          738 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LEUKOTRIENE ANTAGONISTS+OLD/CT

L2          266 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "LEUKOTRIENE RECEPTORS (L)
                LEUKOTRIENE B4"+OLD/CT
L3         4657 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LEUKOTRIENE B4/CT
L5         1618 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "CYCLOOXYGENASE 2"/CT
L8            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "TAISHO NS 398"/CN
L9            3 SEA FILE=REGISTRY ABB=ON  PLU=ON  (MELOXICAM/CN OR "MELOXICAM
                MEGLUMINE"/CN OR "MELOXICAM SODIUM"/CN)
L10           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  FLOCULIDE/CN
L11           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  FLOSULIDE/CN
L12           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "MK 966"/CN
L13           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "L 752860"/CN
L18           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "BAY-X 1005"/CN
L19           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "CGS 25019C"/CN
L20           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  (EBSELEN/CN OR "EBSELEN
```

```
                SELENOXIDE"/CN)
L21             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "ETH 615"/CN
L22             2 SEA FILE=REGISTRY ABB=ON  PLU=ON  ("LY 293111"/CN OR "LY
                  293111 SODIUM SALT"/CN)
L23             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "ONO 4057"/CN
L24             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "TMK 688"/CN
L25             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "BIRM 270"/CN
L26             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "LY 213024"/CN
L27             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "LY 264086"/CN
L28             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "LY 292728"/CN
L29             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "ONO-LB 457"/CN
L30             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PFIZER 105696"/CN
L31             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PF 10042"/CN
L32             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "RP 66153"/CN
L33             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "SB 201146"/CN
L34             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "SB 201993"/CN
L35             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "SC 53228"/CN
L36             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "SM 15178"/CN
L37             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "WAY 121006"/CN
L38            54 SEA FILE=REGISTRY ABB=ON  PLU=ON  "8276"
L39           902 SEA FILE=REGISTRY ABB=ON  PLU=ON  "BAY" OR "BAY-O" OR "BAYO"
L40             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L38 AND L39
L41             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "CI 987"/CN
L42             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "L 651392"/CN
L43             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "LY 210073"/CN
L44             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "LY 223982"/CN
L45             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "LY 233569"/CN
L46             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "LY 255283"/CN
L47             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "MK 591"/CN
L48             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "MK 886"/CN
L49             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "ONO-LB 448"/CN
L50             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PF 5901"/CN
L51             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "RG 14893"/CN
L52             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "RP 66364"/CN
L53             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "RP 69698"/CN
L54             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "SC 41930"/CN
L55             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "SC 50505"/CN
L56             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "SC 51146"/CN
L57             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "SKF 104493"/CN
L58             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "TEI 1338"/CN
L59            55 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L8 OR L9 OR L10 OR L11 OR
                  L12 OR L13) AND (L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24
                  OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33
                  OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40 OR L41 OR L42
                  OR L43 OR L44 OR L45 OR L46 OR L47 OR L48 OR L49 OR L50 OR L51
                  OR L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58)
L60            25 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L59 AND ((L1 OR L2 OR L3) OR
                  L5)


=> s l7 or l60
L87            38 L7 OR L60

=> b medline
FILE 'MEDLINE' ENTERED AT 12:27:27 ON 06 NOV 2002

 FILE LAST UPDATED: 5 NOV 2002 (20021105/UP).  FILE COVERS 1958 TO DATE.
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On June 9, 2002, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

If you received SDI results from MEDLINE on October 8, 2002, these may have included old POPLINE data and in some cases duplicate abstracts. For further information on this situation, please visit NLM at: http://www.nlm.nih.gov/pubs/techbull/so02/so02_popline.html

To correct this problem, CAS will remove the POPLINE records from the MEDLINE file and process the SDI run dated October 8, 2002 again.

Customers who received SDI results via email or hard copy prints on October 8, 2002 will not be charged for this SDI run. If you received your update online and displayed answers, you may request a credit by contacting the CAS Help Desk at 1-800-848-6533 in North America or 614-447-3698 worldwide, or via email to help@cas.org

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> d que l68
L61         7101 SEA FILE=MEDLINE ABB=ON  PLU=ON  CYCLOOXYGENASE INHIBITORS/CT
L62          934 SEA FILE=MEDLINE ABB=ON  PLU=ON  LEUKOTRIENE ANTAGONISTS/CT
L63          276 SEA FILE=MEDLINE ABB=ON  PLU=ON  "LEUKOTRIENE B4: AI, ANTAGONIS
                 TS & INHIBITORS"/CT
L64          332 SEA FILE=MEDLINE ABB=ON  PLU=ON  "RECEPTORS, LEUKOTRIENE
                 B4"/CT
L65         4330 SEA FILE=MEDLINE ABB=ON  PLU=ON  LEUKOTRIENE B4/CT
L66          276 SEA FILE=MEDLINE ABB=ON  PLU=ON  L65(L)(AI OR ANTAG? OR
                 INHIB?)
L67          176 SEA FILE=MEDLINE ABB=ON  PLU=ON  L61 AND (L62 OR L63 OR L64 OR
                 L65 OR L66)
L68           18 SEA FILE=MEDLINE ABB=ON  PLU=ON  L67 AND (COX2 OR COXII OR
                 COX(W)(2 OR II) OR CYCLOOXYGENASE(W)(2 OR II))


=> d que l80
L73          677 SEA FILE=EMBASE ABB=ON  PLU=ON  BAYX 1005 OR BAY X 1005 OR
                 BAYX1005 OR CBS 25019C OR CBS25019C OR EBSELEN OR ETH615 OR
                 ETH 615 OR LY293111 OR LY 293111 OR ONO 4057 OR ONO4057 OR
                 TMK688 OR TMK 688 OR BI RM 270 OR BIRM 270 OR BIRM270 OR
                 LY213024 OR LY 213024 OR LY264086 OR LY 264086 OR LY292728 OR
                 LY 292728 OR ONOLB457
L74          109 SEA FILE=EMBASE ABB=ON  PLU=ON  ONO LB457 OR 105696 OR PF
                 10042 OR PF10042 OR RP66153 OR RP 66153 OR SB201146 OR SB
                 201146 OR SB201993 OR SB 201993 OR SC53228 OR SC 53228 OR
                 SM15178 OR SM15178 OR WAY121006 OR WAY 121006 OR BY O 8276 OR
                 BAY 0 8276 OR BAY 08276 OR BAY08276 OR CI 987 OR CI987 OR
                 L651392 OR L 651392
L75          657 SEA FILE=EMBASE ABB=ON  PLU=ON  LY210073 OR LY 210073 OR
                 LY223982 OR LY 223982 OR LY233569 OR LY 233569 OR LY255283 OR
                 LY 255283 OR MK591 OR MK 591 OR MK886 OR MK 886 OR ONOLB448 OR
                 LB 448 OR PF5901 OR PF 5901 OR RG14893 OR RG 14893 OR RP66364
                 OR RP 66364 OR RP69698 OR RP 69698 OR SC41930 OR SC 41930
L76           10 SEA FILE=EMBASE ABB=ON  PLU=ON  SC50505 OR SC 50505 OR SC51146
                 OR SC 51146 OR SKF 104493 OR SKF104493 OR TEI1338 OR TEI 1338
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L78        1052 SEA FILE=MEDLINE ABB=ON  PLU=ON  NS398 OR NS 398 OR MELOXICAM
                OR FLOCULIDE OR FLOSULIDE OR MK966 OR MK 966 OR L752860 OR L
                752860 OR L 752 860
L79         907 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L73 OR L74 OR L75 OR L76)
L80           8 SEA FILE=MEDLINE ABB=ON  PLU=ON  L78 AND L79


=> s l68 or l80
L88          24 L68 OR L80

=> b embase
FILE 'EMBASE' ENTERED AT 12:28:00 ON 06 NOV 2002
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 FILE COVERS 1974 TO 31 Oct 2002 (20021031/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l77
L69        2716 SEA FILE=EMBASE ABB=ON  PLU=ON  CYCLOOXYGENASE 2 INHIBITOR/CT
L70         143 SEA FILE=EMBASE ABB=ON  PLU=ON  LEUKOTRIENE B4 RECEPTOR
                ANTAGONIST/CT
L72        1671 SEA FILE=EMBASE ABB=ON  PLU=ON  NS398 OR NS 398 OR MELOXICAM
                OR FLOCULIDE OR FLOSULIDE OR MK966 OR MK 966 OR L752860 OR L
                752860 OR L 752 860
L73         677 SEA FILE=EMBASE ABB=ON  PLU=ON  BAYX 1005 OR BAY X 1005 OR
                BAYX1005 OR CBS 25019C OR CBS25019C OR EBSELEN OR ETH615 OR
                ETH 615 OR LY293111 OR LY 293111 OR ONO 4057 OR ONO4057 OR
                TMK688 OR TMK 688 OR BI RM 270 OR BIRM 270 OR BIRM270 OR
                LY213024 OR LY 213024 OR LY264086 OR LY 264086 OR LY292728 OR
                LY 292728 OR ONOLB457
L74         109 SEA FILE=EMBASE ABB=ON  PLU=ON  ONO LB457 OR 105696 OR PF
                10042 OR PF10042 OR RP66153 OR RP 66153 OR SB201146 OR SB
                201146 OR SB201993 OR SB 201993 OR SC53228 OR SC 53228 OR
                SM15178 OR SM15178 OR WAY121006 OR WAY 121006 OR BY O 8276 OR
                BAY 0 8276 OR BAY 08276 OR BAY08276 OR CI 987 OR CI987 OR
                L651392 OR L 651392
L75         657 SEA FILE=EMBASE ABB=ON  PLU=ON  LY210073 OR LY 210073 OR
                LY223982 OR LY 223982 OR LY233569 OR LY 233569 OR LY255283 OR
                LY 255283 OR MK591 OR MK 591 OR MK886 OR MK 886 OR ONOLB448 OR
                LB 448 OR PF5901 OR PF 5901 OR RG14893 OR RG 14893 OR RP66364
                OR RP 66364 OR RP69698 OR RP 69698 OR SC41930 OR SC 41930
L76          10 SEA FILE=EMBASE ABB=ON  PLU=ON  SC50505 OR SC 50505 OR SC51146
                OR SC 51146 OR SKF 104493 OR SKF104493 OR TEI1338 OR TEI 1338
L77          23 SEA FILE=EMBASE ABB=ON  PLU=ON  (L69 OR L72) AND (L70 OR (L73
                OR L74 OR L75 OR L76))


=> b drugu
FILE 'DRUGU' ENTERED AT 12:28:14 ON 06 NOV 2002
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FILE LAST UPDATED: 6 NOV 2002       <20021106/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<
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>>>  SDI'S MAY BE RUN WEEKLY OR MONTHLY AS OF JUNE 2001.  <<<
>>>  (WEEKLY IS THE DEFAULT). FOR PRICING INFORMATION     <<<
>>>  SEE HELP COST                                        <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<


=> d que l83
L72         1671 SEA FILE=EMBASE ABB=ON  PLU=ON  NS398 OR NS 398 OR MELOXICAM
                 OR FLOCULIDE OR FLOSULIDE OR MK966 OR MK 966 OR L752860 OR L
                 752860 OR L 752 860
L73          677 SEA FILE=EMBASE ABB=ON  PLU=ON  BAYX 1005 OR BAY X 1005 OR
                 BAYX1005 OR CBS 25019C OR CBS25019C OR EBSELEN OR ETH615 OR
                 ETH 615 OR LY293111 OR LY 293111 OR ONO 4057 OR ONO4057 OR
                 TMK688 OR TMK 688 OR BI RM 270 OR BIRM 270 OR BIRM270 OR
                 LY213024 OR LY 213024 OR LY264086 OR LY 264086 OR LY292728 OR
                 LY 292728 OR ONOLB457
L74          109 SEA FILE=EMBASE ABB=ON  PLU=ON  ONO LB457 OR 105696 OR PF
                 10042 OR PF10042 OR RP66153 OR RP 66153 OR SB201146 OR SB
                 201146 OR SB201993 OR SB 201993 OR SC53228 OR SC 53228 OR
                 SM15178 OR SM15178 OR WAY121006 OR WAY 121006 OR BY O 8276 OR
                 BAY 0 8276 OR BAY 08276 OR BAY08276 OR CI 987 OR CI987 OR
                 L651392 OR L 651392
L75          657 SEA FILE=EMBASE ABB=ON  PLU=ON  LY210073 OR LY 210073 OR
                 LY223982 OR LY 223982 OR LY233569 OR LY 233569 OR LY255283 OR
                 LY 255283 OR MK591 OR MK 591 OR MK886 OR MK 886 OR ONOLB448 OR
                 LB 448 OR PF5901 OR PF 5901 OR RG14893 OR RG 14893 OR RP66364
                 OR RP 66364 OR RP69698 OR RP 69698 OR SC41930 OR SC 41930
L76           10 SEA FILE=EMBASE ABB=ON  PLU=ON  SC50505 OR SC 50505 OR SC51146
                 OR SC 51146 OR SKF 104493 OR SKF104493 OR TEI1338 OR TEI 1338
L81         3583 SEA FILE=DRUGU ABB=ON  PLU=ON  (COX2 OR COXII OR COX(W)(2 OR
                 II) OR CYCLOOXYGENASE(W)(2 OR II))(3A)(ANTAG? OR INHIB?) OR
                 L72
L82         1099 SEA FILE=DRUGU ABB=ON  PLU=ON  LEUKOTRIENE B4(3A)(ANTAG? OR
                 INHIB?) OR (L73 OR L74 OR L75 OR L76)
L83           21 SEA FILE=DRUGU ABB=ON  PLU=ON  L81 AND L82


=> b wpix
FILE 'WPIX' ENTERED AT 12:28:24 ON 06 NOV 2002
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FILE LAST UPDATED:          5 NOV 2002      <20021105/UP>
MOST RECENT DERWENT UPDATE:     200271        <200271/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> SDI run number 70 for WPI was inadvertently processed with
    a wrong ED/UP date resulting in empty answer sets.
    Therefore SDI 70 will be rerun tonight.  <<<

>>> SLART (Simultaneous Left and Right Truncation) is now
    available in the /ABEX field. An additional search field
    /BIX is also provided which comprises both /BI and /ABEX <<<

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
```

SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER GUIDES, PLEASE VISIT:
http://www.derwent.com/userguides/dwpi_guide.html <<<

=> d que l86
L72 1671 SEA FILE=EMBASE ABB=ON PLU=ON NS398 OR NS 398 OR MELOXICAM OR FLOCULIDE OR FLOSULIDE OR MK966 OR MK 966 OR L752860 OR L 752860 OR L 752 860
L73 677 SEA FILE=EMBASE ABB=ON PLU=ON BAYX 1005 OR BAY X 1005 OR BAYX1005 OR CBS 25019C OR CBS25019C OR EBSELEN OR ETH615 OR ETH 615 OR LY293111 OR LY 293111 OR ONO 4057 OR ONO4057 OR TMK688 OR TMK 688 OR BI RM 270 OR BIRM 270 OR BIRM270 OR LY213024 OR LY 213024 OR LY264086 OR LY 264086 OR LY292728 OR LY 292728 OR ONOLB457
L74 109 SEA FILE=EMBASE ABB=ON PLU=ON ONO LB457 OR 105696 OR PF 10042 OR PF10042 OR RP66153 OR RP 66153 OR SB201146 OR SB 201146 OR SB201993 OR SB 201993 OR SC53228 OR SC 53228 OR SM15178 OR SM15178 OR WAY121006 OR WAY 121006 OR BY O 8276 OR BAY 0 8276 OR BAY 08276 OR BAY08276 OR CI 987 OR CI987 OR L651392 OR L 651392
L75 657 SEA FILE=EMBASE ABB=ON PLU=ON LY210073 OR LY 210073 OR LY223982 OR LY 223982 OR LY233569 OR LY 233569 OR LY255283 OR LY 255283 OR MK591 OR MK 591 OR MK886 OR MK 886 OR ONOLB448 OR LB 448 OR PF5901 OR PF 5901 OR RG14893 OR RG 14893 OR RP66364 OR RP 66364 OR RP69698 OR RP 69698 OR SC41930 OR SC 41930
L76 10 SEA FILE=EMBASE ABB=ON PLU=ON SC50505 OR SC 50505 OR SC51146 OR SC 51146 OR SKF 104493 OR SKF104493 OR TEI1338 OR TEI 1338
L84 527 SEA FILE=WPIX ABB=ON PLU=ON (COX2 OR COXII OR COX(W)(2 OR II) OR CYCLOOXYGENASE(W)(2 OR II))(3A)(ANTAG? OR INHIB?) OR L72
L85 154 SEA FILE=WPIX ABB=ON PLU=ON LEUKOTRIENE B4(3A)(ANTAG? OR INHIB?) OR (L73 OR L74 OR L75 OR L76)
L86 7 SEA FILE=WPIX ABB=ON PLU=ON L84 AND L85

=> dup rem l88 l87 l83 l77 l86
FILE 'MEDLINE' ENTERED AT 12:29:07 ON 06 NOV 2002

FILE 'HCAPLUS' ENTERED AT 12:29:07 ON 06 NOV 2002
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FILE 'DRUGU' ENTERED AT 12:29:07 ON 06 NOV 2002
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FILE 'WPIX' ENTERED AT 12:29:07 ON 06 NOV 2002
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PROCESSING COMPLETED FOR L88

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PROCESSING COMPLETED FOR L87
PROCESSING COMPLETED FOR L83
PROCESSING COMPLETED FOR L77
PROCESSING COMPLETED FOR L86
L89          94 DUP REM L88 L87 L83 L77 L86 (19 DUPLICATES REMOVED)

=> s l89 and (cox2 or coxii or cox()(2 or ii) or cyclooxygenase()(2 or ii) or
leukotriene b4)
   4 FILES SEARCHED...
L90          85 L89 AND (COX2 OR COXII OR COX(W)(2 OR II) OR CYCLOOXYGENASE(W)(2
                OR II) OR LEUKOTRIENE B4)

=> s l90 and (antag? or inhib?)
L91          85 L90 AND (ANTAG? OR INHIB?)

=> s l89 and (cox2 or coxii or cox()(2 or ii) or cyclooxygenase()(2 or ii)) and
leukotriene
   4 FILES SEARCHED...
L92          53 L89 AND (COX2 OR COXII OR COX(W)(2 OR II) OR CYCLOOXYGENASE(W)(2
                OR II)) AND LEUKOTRIENE

=> d ibib ab 1-53

L92  ANSWER 1 OF 53     MEDLINE
ACCESSION NUMBER:    2002635732     IN-PROCESS
DOCUMENT NUMBER:     22282061   PubMed ID: 12392782
TITLE:               Cyclooxygenase and 5-lipoxygenase inhibitors protect
                     against mononuclear phagocyte neurotoxicity.
AUTHOR:              Klegeris Andis; McGeer Patrick L
CORPORATE SOURCE:    Kinsmen Laboratory of Neurological Research, University of
                     British Columbia, BC, V6T 1Z3, Vancouver, Canada.
SOURCE:              NEUROBIOLOGY OF AGING, (2002 Sep) 23 (5) 787.
                     Journal code: 8100437. ISSN: 0197-4580.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE:          Entered STN: 20021024
                     Last Updated on STN: 20021024
AB   Neuroinflammation and oxidative stress are believed to be contributing
     factors to neurodegeneration in normal aging, as well as in age-related
     neurological disorders. Reactive microglia are found in increased numbers
     in aging brain and are prominently associated with lesions in such
     age-related degenerative conditions as Alzheimer's disease (AD),
     Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). In
     vitro, stimulated microglia or microglial-like cells secrete neurotoxic
     materials and are generators of free radicals through their respiratory
     burst system. Agents that suppress microglial activation are therefore
     candidates for neuroprotection. We have developed quantitative in vitro
     assays for measuring neurotoxicity of microglia or other mononuclear
     phagocytes. Neuronal like SH-SY5Y cells are cultured in supernatants from
     activated cells of the human monocytic THP-1 line and their survival is
     followed. Respiratory burst is directly measured on the activated cells.
     We tested inhibitors of the cyclooxygenase (COX) or the 5-lipoxygenase
     (5-LOX) pathways as possible neuroprotective agents. The COX pathway
     generates inflammatory prostaglandins, while the 5-LOX pathway generates
     inflammatory leukotrienes. We found that inhibitors of both
     these pathways suppressed neurotoxicity in a dose-dependent fashion. They
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included the COX-1 inhibitor indomethacin; the **COX-2** inhibitor **NS-398**; the mixed COX-1/**COX-2** inhibitor ibuprofen; the nitric oxide (NO) derivatives of indomethacin, ibuprofen and flurbiprofen; the 5-LOX inhibitor REV 5901; and the 5-LOX activating protein (FLAP) inhibitor **MK-886**. The FLAP inhibitor also reduced respiratory burst activity in a more potent manner than indomethacin. Combinations of COX and 5-LOX inhibitors were more effective than single inhibitors. The data suggest that both COX inhibitors and 5-LOX inhibitors may be neuroprotective in vivo by suppressing toxic actions of microglia/macrophages, and that combinations of the two might have greater therapeutic potential than single inhibitors of either class.

L92 ANSWER 2 OF 53 MEDLINE
ACCESSION NUMBER: 2002377888 MEDLINE
DOCUMENT NUMBER: 22119204 PubMed ID: 12124864
TITLE: Study of the role of **leukotriene** B()4 in abnormal function of human subchondral osteoarthritis osteoblasts: effects of cyclooxygenase and/or 5-lipoxygenase inhibition.
AUTHOR: Paredes Yosabeth; Massicotte Frederic; Pelletier Jean-Pierre; Martel-Pelletier Johanne; Laufer Stefan; Lajeunesse Daniel
CORPORATE SOURCE: Centre Hospitalier de l'Universite de Montreal, Hopital Notre-Dame, Montreal, Quebec, Canada.
SOURCE: ARTHRITIS AND RHEUMATISM, (2002 Jul) 46 (7) 1804-12. Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020719
Last Updated on STN: 20020806
Entered Medline: 20020805

AB OBJECTIVE: To compare the effect of licofelone, **NS-398** (an inhibitor of **cyclooxygenase 2** [**COX-2**]), and **BayX-1005** (an inhibitor of 5-lipoxygenase activating protein) on the production of **leukotriene** B(4) (LTB(4)) and prostaglandin E(2) (PGE(2)), and on cell biomarkers by human osteoarthritis (OA) subchondral osteoblasts. METHODS: Primary in vitro osteoblasts were prepared from subchondral bone specimens obtained from OA patients and autopsy subjects. LTB(4) and PGE(2) levels were measured by enzyme-linked immunosorbent assay in conditioned media of osteoblasts incubated in the presence or absence of licofelone, **NS-398**, or **BayX-1005**. The effect of these drugs or of the addition of LTB(4) on alkaline phosphatase (AP) activity and osteocalcin release by OA and normal osteoblasts was determined. The presence of LTB(4) receptors in normal and OA osteoblasts was evaluated by Western blot analysis. RESULTS: OA osteoblasts produced variable levels of PGE(2) and LTB(4) compared with normal osteoblasts. Licofelone, at the maximal dose used, inhibited production of PGE(2) and LTB(4) by OA osteoblasts by a mean +/- SEM of 61.2 +/- 6.4% and 67.0 +/- 7.6%, respectively. **NS-398** reduced PGE(2) production by 75.8 +/- 5.3%. **BayX-1005** inhibited LTB(4) production in OA osteoblasts by 38.7 +/- 14.5% and marginally affected PGE(2) levels (reduction of 14.8 +/- 5.3%). Licofelone dose-dependently stimulated 1,25-dihydroxyvitamin D-induced AP activity while inhibiting osteocalcin release. **BayX-1005** partly

reproduced these effects, but **NS-398** failed to affect them. LTB(4) dose-dependently inhibited AP activity in OA osteoblasts, while its effect on osteocalcin depended on endogenous LTB(4) levels in these cells. In normal osteoblasts, LTB(4) dose-dependently stimulated osteocalcin, whereas it failed to influence AP. LTB(4) receptors BLT1 and BLT2 were present in normal and OA osteoblasts. CONCLUSION: Licofelone inhibits the production of PGE(2) and LTB(4). Selective effects of licofelone on AP and osteocalcin occur via its role on LTB(4) production. Because LTB(4) can modify cell biomarkers in OA and normal osteoblasts, our results suggest licofelone could modify abnormal bone remodeling in OA.

L92 ANSWER 3 OF 53 MEDLINE
ACCESSION NUMBER: 2002176008 MEDLINE
DOCUMENT NUMBER: 21905240 PubMed ID: 11908571
TITLE: Synthesis of interleukin 1beta, tumor necrosis factor-alpha, and interstitial collagenase (MMP-1) is eicosanoid dependent in human osteoarthritis synovial membrane explants: interactions with antiinflammatory cytokines.
AUTHOR: He Wendy; Pelletier Jean-Pierre; Martel-Pelletier Johanne; Laufer Stefan; Di Battista John A
CORPORATE SOURCE: Osteoarthritis Research Unit, Hopital Notre-Dame, Centre Hospitalier de l'Universite de Montreal, Quebec, Canada.
SOURCE: JOURNAL OF RHEUMATOLOGY, (2002 Mar) 29 (3) 546-53. Journal code: 7501984. ISSN: 0315-162X.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020324
Last Updated on STN: 20021008
Entered Medline: 20020924

AB OBJECTIVE: To determine the level of **leukotriene** B4 (LTB4) synthesized and released by synovium of patients with osteoarthritis (OA), and to study the role of lipoxygenase (LO)/cyclooxygenase (COX) products on proinflammatory cytokine and interstitial collagenase (MMP-1) synthesis. METHODS: Human OA synovial explants were cultured in the presence of lipopolysaccharide (L) and the ionophores ionomycin (I) and thapsigargin (T) (LIT) for 72 h at 37 degrees C, and LTB4 released into the culture medium was measured in the absence or presence of a **COX-2**-specific inhibitor, **NS-398**, or the 5-LO activating protein inhibitor **Bay-x-1005**. Increasing concentrations of LTB4 (10(-9) to 10(-6) M) were incubated with explants for 24 h at 37 degrees C, and interleukin 1beta (IL-1beta) and tumor necrosis factor-alpha (TNF-alpha) in the conditioned medium were quantitated by ELISA. The effect of endogenous eicosanoids on basal and induced levels of IL-1beta, TNF-alpha, and MMP-1 synthesis was examined by incubating explants in the presence of **NS-398** and **Bay-x-1005**. The effect of antiinflammatory cytokines rhIL-4, IL-10, and IL-13 on basal and LTB4 dependent stimulation of IL-1beta/TNF-alpha synthesis was studied under titration conditions. RESULTS: Physiologically relevant concentrations (10(-10) to 10(-9) mol/l) of LTB4 were produced in the presence of LIT. **Bay-x-1005** abrogated LTB4 release, while **NS-398** was without effect. LTB4 stimulated IL-1beta and TNF-alpha synthesis with an EC50 of 190 +/- 35 and 45 +/- 9 nmol/l,

respectively. Significant concentrations of IL-1beta and TNF-alpha were released (100-200 and 500-600 pg/ml, respectively). Basal and LIT induced IL-1beta and TNF-alpha production were inhibited by **Bay-x-1005** in a dose dependent manner, while the addition of **NS-398** caused a potent stimulatory effect. The preferential **COX-2** inhibitor also induced MMP-1 synthesis in a manner essentially identical to the proinflammatory cytokines. The antiinflammatory cytokine IL-4 blocked LTB4 dependent stimulation of IL-1beta and TNF-alpha synthesis. In contrast, IL-10 markedly stimulated both cytokines when incubated alone or in the presence of LTB4 where the effect was additive. CONCLUSION: Endogenous and locally produced eicosanoids regulate proinflammatory cytokine and MMP-1 synthesis under basal and stimulated conditions in vitro, with **leukotrienes** and prostaglandins having opposite effects in general. The clinical use of antiinflammatory drugs that inhibit eicosanoid synthesis requires an appreciation of their relative capacity to inhibit LO/COX in order to predict their effect on the synthesis of proinflammatory cytokines and matrix metalloproteases. IL-10 stimulated proinflammatory cytokine synthesis in our ex vivo culture system.

L92 ANSWER 4 OF 53 MEDLINE
ACCESSION NUMBER: 2001444320 MEDLINE
DOCUMENT NUMBER: 21383016 PubMed ID: 11490357
TITLE: Prostaglandin E2 receptors EP2 and EP4 are down-regulated in human mononuclear cells after injury.
AUTHOR: Strong V E; Winter J; Yan Z; Smyth G P; Mestre J R; Maddali S; Schaefer P A; Yurt R W; Stapleton P P; Daly J M
CORPORATE SOURCE: Department of Surgery, New York Presbyterian Hospital-Weill Medical College of Cornell Univerity, New York, NY 10021, USA.
CONTRACT NUMBER: 1RO1 DK50201-0 (NIDDK)
T32 GM08466-06 (NIGMS)
SOURCE: SURGERY, (2001 Aug) 130 (2) 249-55.
Journal code: 0417347. ISSN: 0039-6060.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010910
Entered Medline: 20010906

AB BACKGROUND: Recent characterization of prostaglandin receptor subtypes shows that each is critical to cellular functions and operates through separate signaling pathways that may explain differing effects of prostanoids. This study aimed to determine whether prostaglandin receptors EP2 and EP4 are modulated after injury and to evaluate the effect of prostaglandin E(2) (PGE(2)) addition and blockade on EP receptor expression. METHODS: Peripheral blood mononuclear cells (PBMCs) isolated from 10 patients sustaining fracture or burn injury and 10 control subjects were stimulated with lipopolysaccharide +/- NS-398, an inhibitor of PGE(2) production. Samples were evaluated for production of PGE(2), tumor necrosis factor--alpha, and **leukotriene** B(4) as well as mRNA expression of EP receptors and **COX-2**. EP receptor expression was also evaluated after treating control PBMCs with PGE(2). RESULTS: PBMCs from injured patients exhibited significant increases in PGE(2) production and **COX-2** mRNA compared with control subjects, and these increases were inhibited by NS-398. In contrast, EP2

and EP4 receptors were markedly down-regulated after injury and NS-398 restored expression to control levels. Decreased EP2 and EP4 receptor expression after injury was replicated by coincubation of PBMCs with PGE(2). CONCLUSIONS: Specific PGE(2) receptors are down-regulated after injury and NS-398 reverses this response. Furthermore, PGE(2) mediates EP2 and EP4 down-regulation. These data suggest that specific EP receptor subtypes may provide critical targets for augmenting the immune response after injury in humans.

L92 ANSWER 5 OF 53 MEDLINE
ACCESSION NUMBER: 2001409228 MEDLINE
DOCUMENT NUMBER: 21180744 PubMed ID: 11286400
TITLE: The anti-inflammatory effect of FR188582, a highly selective inhibitor of **cyclooxygenase-2**, with an ulcerogenic sparing effect in rats.
AUTHOR: Ochi T; Yamane-Sugiyama A; Ohkubo Y; Sakane K; Tanaka H
CORPORATE SOURCE: Department of Immunology and Inflammation, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan.. takehiro_ochi@po.fujisawa.co.jp
SOURCE: JAPANESE JOURNAL OF PHARMACOLOGY, (2001 Feb) 85 (2) 175-82. Journal code: 2983305R. ISSN: 0021-5198.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB The anti-inflammatory and ulcerogenic effects of FR188582, 3-chloro-5-[4-(methylsulfonyl) phenyl]-1-phenyl-1H-pyrazole, were investigated. In a recombinant human cyclooxygenase (COX) enzyme activity, FR188582 inhibited **COX-2** with an IC50 value of 0.017 microM, and the inhibition of prostaglandin (PG) E2 formation by FR188582 was over 6000 times more selective for **COX-2** than COX-1. Oral administration of FR188582 dose-dependently inhibited adjuvant arthritis. This effect was threefold more potent than that of indomethacin. FR188582 and indomethacin dose-dependently suppressed the formation of immunoreactive PGE2, but not immunoreactive **leukotriene** (LT) B4, in arthritic paw. Unlike indomethacin, FR188582 did not induce visible gastric lesions in rats at doses up to 32 mg/kg, p.o. Furthermore, FR188582 did not inhibit the level of immunoreactive PGE2 and immunoreactive 6-keto PGF1alpha in rat gastric mucosa. These results suggest that FR188582, a highly selective **COX-2** inhibitor, has a potent anti-inflammatory effect mediated by inhibition of PGE2 in inflamed tissues. The safety profile of FR188582 appears to be improved over the safety profile of indomethacin.

L92 ANSWER 6 OF 53 MEDLINE
ACCESSION NUMBER: 2001277260 MEDLINE
DOCUMENT NUMBER: 21262279 PubMed ID: 11368536
TITLE: NS-398 treatment after trauma modifies NF-kappaB activation and improves survival.
AUTHOR: Mack Strong V E; Mackrell P J; Concannon E M; Mestre J R; Smyth G P; Schaefer P A; Stapleton P P; Daly J M
CORPORATE SOURCE: Department of Surgery, New York Presbyterian Hospital-Weill Medical College of Cornell University, New York, New York 10021, USA.. vem9002@nyp.org

SOURCE: JOURNAL OF SURGICAL RESEARCH, (2001 Jun 1) 98 (1) 40-6.
Journal code: 0376340. ISSN: 0022-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010702
Last Updated on STN: 20010702
Entered Medline: 20010628

AB Prostaglandin E(2) (PGE(2)) production after trauma contributes to immune alterations that increase susceptibility to infections. We hypothesize that blocking PGE(2) with NS-398, a selective **COX-2** inhibitor, will modulate this response and improve outcome. This study evaluated the effect of NS-398 given over 7 days on proinflammatory cytokines, intracellular signaling, and survival after a septic challenge. Balb/C mice (n = 8/group) were given 10 mg/kg NS-398 intraperitoneally over 7 days, starting after anesthesia or trauma (femur fracture + 40% hemorrhage). Four groups, anesthesia + vehicle (C), anesthesia + NS-398 (CN), trauma + vehicle (T), or trauma + NS-398 (TN), were studied. On Day 7 after trauma, mice were sacrificed, serum was collected, and splenic macrophages were evaluated for PGE(2), LTB(4), IL-6, TNF-alpha, and NO production. Additionally, macrophage **COX-2** mRNA, IkappaB-alpha, and NF-kappaB were evaluated. In a separate study, mice (n = 10-11/group) were traumatized and given NS-398 over 7 days, and then cecal ligation and puncture (CLP) were performed. Mice were then followed for survival over 10 days (via log-rank test). NS-398 treatment of injured mice decreased PGE(2) production compared to T (3.9 +/- 0.3 vs 3.1 +/- 0.4 pg/microg protein), and significantly decreased IL-6, NO, and TNF-alpha production. NS-398 treatment also attenuated **COX-2** mRNA levels and NF-kappaB activation. These cellular events correlate with a significant survival advantage in TN versus T mice after CLP. These data suggest that a specific **COX-2** inhibitor not only suppresses PGE(2), but normalizes proinflammatory cytokines after trauma through changes that may partly be mediated via transcriptional events. This correlates with significantly increased survival in TN mice given a septic challenge and suggests that **COX-2** inhibitors contribute to modulating the inflammatory response and improving survival after trauma.

L92 ANSWER 7 OF 53 MEDLINE
ACCESSION NUMBER: 2001166187 MEDLINE
DOCUMENT NUMBER: 21164930 PubMed ID: 11264253
TITLE: Cyclo-oxygenase and lipoxygenase pathways in mast cell dependent-neurogenic inflammation induced by electrical stimulation of the rat saphenous nerve.
AUTHOR: Le Filliatre G; Sayah S; Latournerie V; Renaud J F; Finet M; Hanf R
CORPORATE SOURCE: Service de Pharmacologie, Laboratoire Innothera, 7 - 9 av Francois Vincent Raspail, BP 12, 94111, Arcueil Cedex, France.. gael.le.filliatre@innothera.com
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (2001 Apr) 132 (7) 1581-9.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517

AB 1. We investigated the role of arachidonic acid metabolism and assessed the participation of mast cells and leukocytes in neurogenic inflammation in rat paw skin. We compared the effect of lipoxygenase (LOX) and cyclo-oxygenase (COX) inhibitors on oedema induced by saphenous nerve stimulation, substance P (SP), and compound 48/80. 2. Intravenous (i.v.) pre-treatment with a dual COX/LOX inhibitor (RWJ 63556), a dual LOX inhibitor/cysteinyl-**leukotriene** (CysLt) receptor antagonist (Rev 5901), a LOX inhibitor (AA 861), a five-lipoxygenase activating factor (FLAP) inhibitor (**MK 886**), or a glutathione S-transferase inhibitor (ethacrynic acid) significantly inhibited (40 to 60%) the development of neurogenic oedema, but did not affect cutaneous blood flow. Intradermal (i.d.) injection of LOX inhibitors reduced SP-induced oedema (up to 50% for RWJ 63556 and **MK 886**), whereas ethacrynic acid had a potentiating effect. 3. Indomethacin and rofecoxib, a highly selective **COX-2** inhibitor, did not affect neurogenic and SP-induced oedema. Surprisingly, the structurally related **COX-2** inhibitors, **NS 398** and nimesulide, significantly reduced both neurogenic and SP-induced oedema (70% and 42% for neurogenic oedema, respectively; 49% and 46% for SP-induced oedema, respectively). 4. **COX-2** mRNA was undetectable in saphenous nerves and paw skin biopsy samples, before and after saphenous nerve stimulation. 5. A mast cell stabilizer, cromolyn, and a H(1) receptor antagonist, mepyramine, significantly inhibited neurogenic (51% and 43%, respectively) and SP-induced oedema (67% and 63%, respectively). 6. The co-injection of LOX inhibitors and compound 48/80 did not alter the effects of compound 48/80. Conversely, ethacrynic acid had a significant potentiating effect. The pharmacological profile of the effect of COX inhibitors on compound 48/80-induced oedema was similar to that of neurogenic and SP-induced oedema. 7. The polysaccharide, fucoidan (an inhibitor of leukocyte rolling) did not affect neurogenic or SP-induced oedema. 8. Thus, (i) SP-induced **leukotriene** synthesis is involved in the development of neurogenic oedema in rat paw skin; (ii) this **leukotriene**-mediated plasma extravasation might be independent of mast cell activation and/or of the adhesion of leukocytes to the endothelium; (iii) COX did not appear to play a significant role in this process.

L92 ANSWER 8 OF 53 MEDLINE
ACCESSION NUMBER: 2001108965 MEDLINE
DOCUMENT NUMBER: 21065672 PubMed ID: 11137876
TITLE: Protective role of cyclooxygenase inhibitors in the adverse action of passive cigarette smoking on the initiation of experimental colitis in rats.
AUTHOR: Guo X; Liu E S; Ko J K; Wong B C; Ye Y; Lam S; Cho C
CORPORATE SOURCE: Department of Pharmacology, Faculty of Medicine, The University of Hong Kong, 1/F, Li Shu Fan Bldg., 5 Sassoon Road, SAR, Hong Kong, People's Republic of China.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (2001 Jan 5) 411 (1-2) 193-203.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010208

AB Clinical and experimental findings had indicated that cigarette smoke exposure, and **cyclooxygenase-2**, are strongly associated with inflammatory bowel disease. The present study aimed to evaluate the role of **cyclooxygenase-2** in the pathogenesis of experimental inflammatory bowel disease as well as in the adverse action of cigarette-smoke exposure. Rats were pretreated with different **cyclooxygenase-2** inhibitors (indomethacin, nimesulide, or SC-236 (4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide)) along with cigarette-smoke exposure before 2,4,6-trinitrobenzenesulfonic acid-enema. Results indicated that pretreatment with **cyclooxygenase-2** inhibitors not only protected against 2,4,6-trinitrobenzenesulfonic acid-induced inflammatory bowel disease, but also attenuated the potentiating effect of cigarette-smoke exposure on colonic damage. Furthermore, the colonic **cyclooxygenase-2** protein and mRNA expression was markedly induced by 2,4,6-trinitrobenzenesulfonic acid-enema, and it was potentiated further by cigarette-smoke exposure, while the cyclooxygenase-1 expression was not changed. The present study suggests that the highly induced **cyclooxygenase-2** expression not only plays a pathogenic role in 2,4,6-trinitrobenzenesulfonic acid-induced inflammatory bowel disease, but also contributes to the adverse action of cigarette-smoke exposure on this disorder.

L92 ANSWER 9 OF 53 MEDLINE
ACCESSION NUMBER: 2000281736 MEDLINE
DOCUMENT NUMBER: 20281736 PubMed ID: 10821716
TITLE: Novel antiarthritic agents with 1,2-isothiazolidine-1,1-dioxide (gamma-sultam) skeleton: cytokine suppressive dual inhibitors of **cyclooxygenase-2** and 5-lipoxygenase.
AUTHOR: Inagaki M; Tsuri T; Jyoyama H; Ono T; Yamada K; Kobayashi M; Hori Y; Arimura A; Yasui K; Ohno K; Kakudo S; Koizumi K; Suzuki R; Kawai S; Kato M; Matsumoto S
CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553-0002, Japan.
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (2000 May 18) 43 (10) 2040-8.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000706
Last Updated on STN: 20000706
Entered Medline: 20000629

AB Various 1,2-isothiazolidine-1,1-dioxide (gamma-sultam) derivatives containing an antioxidant moiety, 2,6-di-tert-butylphenol substituent, were prepared. Some compounds, which have a lower alkyl group at the 2-position of the gamma-sultam skeleton, showed potent inhibitory effects on both cyclooxygenase (**COX**)-**2** and 5-lipoxygenase (5-LO), as well as production of interleukin (IL)-1 in in vitro assays. They also proved to be effective in several animal arthritic models without any ulcerogenic activities. Among these compounds,

(E)-(5)-(3,5-di-tert-butyl-4-hydroxybenzylidene)-2-ethyl-1, 2-isothiazolidine-1,1-dioxide (S-2474) was selected as an antiarthritic drug candidate and is now under clinical trials. The structure-activity relationships (SAR) examined and some pharmacological evaluations are described.

L92 ANSWER 10 OF 53 MEDLINE
ACCESSION NUMBER: 2000162186 MEDLINE
DOCUMENT NUMBER: 20162186 PubMed ID: 10698360
TITLE: Effects of some isoxazolpyrimidine derivatives on nitric oxide and eicosanoid biosynthesis.
AUTHOR: Vidal A; Ferrandiz M L; Ubeda A; Guillen I; Riguera R; Quintela J M; Peinador C; Moreira M J; Alcaraz M J
CORPORATE SOURCE: Department of Pharmacology, University of Valencia, Spain.
SOURCE: LIFE SCIENCES, (2000 Jan 21) 66 (9) PL125-31. Journal code: 0375521. ISSN: 0024-3205.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000316

AB The inhibitory effect of some isoxazolpyrimidine derivatives on iNOS and **COX-2** endotoxin induction in mouse peritoneal macrophages has been studied. Three of these compounds inhibited nitrite and PGE2 accumulation in a concentration dependent-manner at microM range. None of these active compounds affected iNOS, **COX-2**, COX-1 or PLA2 activities, although some reduced iNOS or **COX-2** expression. Besides, no effect was observed on human neutrophil inflammatory responses (LTB4 biosynthesis and superoxide or elastase release). Active compounds were assayed by oral administration in the mouse air pouch model, where they inhibited nitrite accumulation without affecting PGE2 levels or leukocyte migration.

L92 ANSWER 11 OF 53 MEDLINE
ACCESSION NUMBER: 2000132598 MEDLINE
DOCUMENT NUMBER: 20132598 PubMed ID: 10669114
TITLE: Eicosanoid release in the endotoxin-primed isolated perfused rat lung and its pharmacological modification.
AUTHOR: Amann R; Schuligoi R; Peskar B A
CORPORATE SOURCE: Department of Experimental and Clinical Pharmacology, University of Graz, Austria.. rainer.amann@kfunigraz.ac.at
SOURCE: INFLAMMATION RESEARCH, (1999 Dec) 48 (12) 632-6. Journal code: 9508160. ISSN: 1023-3830.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000320
Last Updated on STN: 20000320
Entered Medline: 20000306

AB OBJECTIVE: Recent observations have demonstrated a central role of the "inducible" isoform of the cyclooxygenase (COX), **COX-2**, in the rat lung. Therefore, the reported capacity of selective **COX-2** inhibitors to potentiate the formation of

leukotriene (LT) B4 may raise concern about pro-inflammatory side effects of such drugs in the respiratory system. The present study was aimed at determining the effects of the **COX-2** inhibitor **NS-398** on the release of COX and 5-lipoxygenase (LOX) metabolites of arachidonic acid in isolated perfused lungs obtained from endotoxin-treated rats before and after stimulation with the leukocyte secretagogue N-formyl-methionyl-leucyl-phenylalanine (FMLP). METHODS: Two hours after rats had received endotoxin i.v., the lung was dissected and perfused via the pulmonary artery with physiological salt solution. After an equilibration period of 20 min the outflow was collected (5-min fractions). In the respective treatment groups, indomethacin, **NS-398**, or the 5-LOX inhibitor **MK886** were present throughout the experiment, while FMLP was added to the perfusate during a single 5-min period. The concentration of eicosanoids in the outflow was determined by radioimmunoassay. RESULTS: Endotoxin treatment of rats resulted in increased expression of **COX-2** mRNA in lung tissue, and an elevated basal release of the prostaglandin (PG)I2 metabolite 6-keto PGF1alpha, without a detectable increase of **leukotriene** (LT) formation. In-vitro exposure to FMLP stimulated LT and prostanoid release, which was significantly enhanced in endotoxin-primed lungs, and was suppressed by the 5-LOX inhibitor **MK-886** (3 microM) and the COX-inhibitor indomethacin (5 microM), respectively. Either compound showed selective inhibition of the respective pathway of arachidonic acid metabolism. In endotoxin-primed lungs, the **COX-2** inhibitor **NS-398** (0.3-1.0 microM) depressed basal as well as FMLP-stimulated release of 6-keto PGF1alpha, but did not cause a significant increase of LTB4 or cysteinyl-LT release. CONCLUSIONS: These results suggest that FMLP, presumably acting on inflammatory cells trapped in the pulmonary circulation of endotoxin treated rats, induced prostanoid formation mainly via the **COX-2** pathway, and that its inhibition by **NS-398** had no detectable potentiating effect on LTB4 or cysteinyl-LT biosynthesis.

L92 ANSWER 12 OF 53 MEDLINE
ACCESSION NUMBER: 1999413014 MEDLINE
DOCUMENT NUMBER: 99413014 PubMed ID: 10483516
TITLE: New insights in the bronchodilatory and anti-inflammatory mechanisms of action of theophylline.
AUTHOR: Juergens U R; Degenhardt V; Stober M; Vetter H
CORPORATE SOURCE: Department of Pulmonary Diseases, Medical Policlinic, University Hospital, Bonn, Germany.
SOURCE: ARZNEIMITTEL-FORSCHUNG, (1999 Aug) 49 (8) 694-8. Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991014 Last Updated on STN: 19991014 Entered Medline: 19991007

AB Phosphodiesterase (PDE) inhibition and adenosine antagonism have been identified as important underlying mechanisms for the bronchodilating and anti-inflammatory action of theophylline (CAS 58-55-9). The aim of the present study was to determine the effects of PDE inhibition by theophylline on cAMP and arachidonic acid (AA) metabolism, namely

leukotriene B4 (LTB4) and prostaglandin E2 (PGE2) production, in cultured monocytes in vitro. Monocytes obtained from healthy non-smoking subjects were incubated in adherence at 37 degrees C for 4 h in the presence of theophylline (0.18, 1.8 and 18 micrograms/ml, respectively) and stimulated with LPS (10 micrograms/ml). LTB4, PGE2 and cAMP were measured in the same culture supernatants by direct enzyme immunoassay. LPS-stimulated generation of cAMP increased significantly (+162%) in the presence of theophylline (18 micrograms/ml); production of LTB4 was suppressed (-42%) compared to the baseline, whereas PGE2 production increased significantly (+39%). Production of cAMP correlated with increased PGE2 production (r = 0.73, p = 0.025) and with suppression of LTB4 (r = 0.67, p = 0.016). These effects were mimicked by cell permeant nucleotides, such as dibutyryl-cAMP but not by dibutyryl-cGMP and could be abolished by ibuprofen. These results provide the first evidence that the clinical efficacy of theophylline may result from inhibition of **leukotriene** production and its capacity to stimulate PGE2 production. The underlying mechanism is suggested as feedback regulatory induction of **COX-2** by a prostaglandin driven cAMP-mediated process.

L92 ANSWER 13 OF 53 MEDLINE
ACCESSION NUMBER: 1999340153 MEDLINE
DOCUMENT NUMBER: 99340153 PubMed ID: 10411562
TITLE: Rofecoxib [Vioxx, MK-0966; 4-(4'-methylsulfonylphenyl)-3-phenyl-2-(5H)-furanone]: a potent and orally active **cyclooxygenase-2** inhibitor. Pharmacological and biochemical profiles.
AUTHOR: Chan C C; Boyce S; Brideau C; Charleson S; Cromlish W; Ethier D; Evans J; Ford-Hutchinson A W; Forrest M J; Gauthier J Y; Gordon R; Gresser M; Guay J; Kargman S; Kennedy B; Leblanc Y; Leger S; Mancini J; O'Neill G P; Ouellet M; Patrick D; Percival M D; Perrier H; Prasit P; Rodger I; +
CORPORATE SOURCE: Departments of Pharmacology, Biochemistry and Molecular Biology, and Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, Kirkland, Quebec, Canada.. chi_chung_chan@merck.com
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1999 Aug) 290 (2) 551-60. Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990827
Last Updated on STN: 19990827
Entered Medline: 19990818

AB The discoveries that cyclooxygenase (**COX**)-**2** is an inducible form of COX involved in inflammation and that COX-1 is the major isoform responsible for the production of prostaglandins (PGs) in the gastrointestinal tract have provided a rationale for the development of specific **COX-2** inhibitors as a new class of anti-inflammatory agents with improved gastrointestinal tolerability. In the present study, the preclinical pharmacological and biochemical profiles of rofecoxib [Vioxx, also known as MK-0966, 4-(4'-methylsulfonylphenyl)-3-phenyl-2-(5H)-furanone], an orally active **COX-2** inhibitor, are described. Rofecoxib is a potent

inhibitor of the **COX-2**-dependent production of PGE(2) in human osteosarcoma cells (IC(50) = 26 +/- 10 nM) and Chinese hamster ovary cells expressing human **COX-2** (IC(50) = 18 +/- 7 nM) with a 1000-fold selectivity for the inhibition of **COX-2** compared with the inhibition of COX-1 activity (IC(50) > 50 microM in U937 cells and IC(50) > 15 microM in Chinese hamster ovary cells expressing human COX-1). Rofecoxib is a time-dependent inhibitor of purified human recombinant **COX-2** (IC(50) = 0.34 microM) but caused inhibition of purified human COX-1 in a non-time-dependent manner that could only be observed at a very low substrate concentration (IC(50) = 26 microM at 0.1 microM arachidonic acid concentration). In an in vitro human whole blood assay, rofecoxib selectively inhibited lipopolysaccharide-induced, **COX-2** -derived PGE(2) synthesis with an IC(50) value of 0.53 +/- 0.02 microM compared with an IC(50) value of 18.8 +/- 0.9 microM for the inhibition of COX-1-derived thromboxane B(2) synthesis after blood coagulation. Using the ratio of the COX-1 IC(50) values over the **COX-2** IC(50) values in the human whole blood assay, selectivity ratios for the inhibition of **COX-2** of 36, 6.6, 2, 3, and 0.4 were obtained for rofecoxib, celecoxib, meloxicam, diclofenac, and indomethacin, respectively. In several in vivo rodent models, rofecoxib is a potent inhibitor of carrageenan-induced paw edema (ID(50) = 1.5 mg/kg), carrageenan-induced paw hyperalgesia (ID(50) = 1.0 mg/kg), lipopolysaccharide-induced pyresis (ID(50) = 0.24 mg/kg), and adjuvant-induced arthritis (ID(50) = 0.74 mg/kg/day). Rofecoxib also has a protective effect on adjuvant-induced destruction of cartilage and bone structures in rats. In a (51)Cr excretion assay for detection of gastrointestinal integrity in either rats or squirrel monkeys, rofecoxib has no effect at doses up to 200 mg/kg/day for 5 days. Rofecoxib is a novel **COX-2** inhibitor with a biochemical and pharmacological profile clearly distinct from that of current nonsteroidal anti-inflammatory drugs and represents a new therapeutic class of anti-inflammatory agents for the treatment of the symptoms of osteoarthritis and rheumatoid arthritis with improved gastrointestinal tolerability.

L92 ANSWER 14 OF 53 MEDLINE
ACCESSION NUMBER: 1999276002 MEDLINE
DOCUMENT NUMBER: 99276002 PubMed ID: 10348246
TITLE: Role of eicosanoids in the pathogenesis of murine cerebral malaria.
AUTHOR: Xiao L; Patterson P S; Yang C; Lal A A
CORPORATE SOURCE: Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30341-3724, USA.
SOURCE: AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE, (1999 Apr) 60 (4) 668-73.
Journal code: 0370507. ISSN: 0002-9637.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990618
Last Updated on STN: 19990618
Entered Medline: 19990608

AB Because microvascular damage is a common feature of cerebral malaria, we have examined the role eicosanoid metabolites (prostaglandins and

leukotrienes) in experimental cerebral malaria. Eighty ICR mice were infected with Plasmodium berghei ANKA, with 40 uninfected mice as controls. Half of the infected mice were treated on days 4 and 5 with aspirin, a prostaglandin synthesis inhibitor. Infected mice started to die of cerebral malaria on day 6, and by day 17, all infected mice died. In contrast, all infected mice treated with aspirin died by day 12. Infected mice had increased phospholipase A2 mRNA expression in the spleen and cyclooxygenase 1 (COX1) and **COX2** expression in the brain. At the peak of cerebral malaria, infected mice had higher serum **leukotriene** B4 levels than control mice, and aspirin-treated infected mice had higher serum **leukotriene** B4 levels than untreated infected mice. These results suggest that prostaglandins are protective whereas **leukotrienes** are detrimental in cerebral malaria.

L92 ANSWER 15 OF 53 MEDLINE
ACCESSION NUMBER: 1999247907 MEDLINE
DOCUMENT NUMBER: 99247907 PubMed ID: 10229670
TITLE: Fish macrophages express a cyclo-oxygenase-2 homologue after activation.
AUTHOR: Zou J; Neumann N F; Holland J W; Belosevic M; Cunningham C; Secombes C J; Rowley A F
CORPORATE SOURCE: Department of Zoology, University of Aberdeen, Aberdeen, AB24 2TZ, UK.
SOURCE: BIOCHEMICAL JOURNAL, (1999 May 15) 340 (Pt 1) 153-9. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990714
Last Updated on STN: 19990714
Entered Medline: 19990630

AB In mammals, the increased generation of prostaglandins (PG) during the onset of inflammatory responses and activation of immune cell types has been attributed to the induction of a novel cyclo-oxygenase (COX) isoform, termed **COX-2**, which is distinct from the well-characterized constitutive activity (COX-1). Goldfish (Carassius auratus) macrophages exposed to bacterial lipopolysaccharide and leucocyte-derived macrophage-activating factor(s) showed a significant increase in the generation of the major COX product, PGE2, within the first 6 h of stimulation. The selective **COX-2** inhibitor, NS398, inhibited this elevated generation of PGE, whereas the basal level of this product synthesized by unstimulated macrophages was unaffected by such exposure. PGE generation by goldfish macrophages was similarly inhibited by the glucocorticoid, dexamethasone, and an inhibitor of protein synthesis, cycloheximide, suggesting that this stimulation may be due to an inducible enzyme equivalent to mammalian **COX-2**. The complete coding sequence of rainbow trout (Oncorhynchus mykiss) **COX-2** was obtained by PCR. The gene contains a 61 bp 5'-untranslated region (UTR), a 1821 bp open reading frame and a 771 bp 3'UTR containing multiple copies of an mRNA instability motif (ATTTA). The predicted translation product had high homology to known mammalian and chicken **COX-2** (83-84%) and COX-1 (77%) sequences. Reverse-transcriptase PCR with cDNA from control and bacterially challenged fish revealed that trout **COX-2** expression was not constitutive but could be induced. Overall, these studies show for

the first time that the inducible isoform of COX has a long evolutionary history, probably dating back to the evolution of fish over 500 million years ago.

L92 ANSWER 16 OF 53 MEDLINE
ACCESSION NUMBER: 1999143821 MEDLINE
DOCUMENT NUMBER: 99143821 PubMed ID: 9989276
TITLE: Eicosanoid biosynthesis in an advanced deuterostomate invertebrate, the sea squirt (Ciona intestinalis).
AUTHOR: Knight J; Taylor G W; Wright P; Clare A S; Rowley A F
CORPORATE SOURCE: School of Biological Sciences, University of Wales Swansea, Singleton Park, UK.
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1999 Jan 4) 1436 (3) 467-78.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990316
Last Updated on STN: 19990316
Entered Medline: 19990304

AB The eicosanoid generating potential of tunic, branchial basket, intestine, ovary and tadpole larvae from the sea squirt, Ciona intestinalis, was examined using a combination of reverse phase high performance liquid chromatography, gas chromatography-mass spectrometry and enzyme immunoassay. All organs examined synthesized the lipoxygenase products 12-hydroxyeicosapentaenoic acid (12-HEPE) and 8-HEPE implying that both 8- and 12-lipoxygenase activity are widely distributed in this species. In addition, tunic and branchial basket generated significant amounts of 8,15-diHEPE and smaller amounts of 8,15-dihydroxyeicosatetraenoic acid (8,15-diHETE), while tunic alone generated small amounts of conjugated tetraene-containing material with a UV chromophore and mass ion characteristic of a lipoxin-like compound. The broad range lipoxygenase inhibitors, esculetin and nordihydroguaiaretic acid, both caused a significant dose dependent inhibition of 12-HEPE and 8,15-diHEPE biosynthesis in tunic, while the specific 5-lipoxygenase inhibitor, REV-5901, and the specific 5-lipoxygenase activating protein inhibitor, MK-866, had no observable effect on the lipoxygenase profile of this tissue. Tunic, branchial basket, intestine and ovary all generated significant amounts of prostaglandin (PG) E and PGF immunoreactive material and smaller amounts of thromboxane B immunoreactive material as measured by enzyme immunoassay. The non-specific cyclooxygenase (COX) inhibitor, indomethacin, the selective COX-1 inhibitors, resveratrol and valerylsalicylate, and the specific **COX-2** inhibitors, NS-398, etolodac and DFU (5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl) phenyl-2(5H)-furanone) all caused a significant dose dependent inhibition of the biosynthesis of PGE immunoreactive material. However, the specific **COX-2** inhibitors were most effective, perhaps implying that a **COX-2**-like enzyme may be present in this species.

L92 ANSWER 17 OF 53 MEDLINE
ACCESSION NUMBER: 1999088895 MEDLINE
DOCUMENT NUMBER: 99088895 PubMed ID: 9871729
TITLE: Synthesis and anti-inflammatory activity of chalcone derivatives.

AUTHOR: Herencia F; Ferrandiz M L; Ubeda A; Dominguez J N; Charris J E; Lobo G M; Alcaraz M J
CORPORATE SOURCE: Departamento de Farmacologia, Universidad de Valencia, Spain.
SOURCE: BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, (1998 May 19) 8 (10) 1169-74.
Journal code: 9107377. ISSN: 0960-894X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990125

AB Chalcones and their derivatives were synthesized and evaluated for their anti-inflammatory activity. In vitro, chalcones 2, 4, 8, 10 and 13 inhibited degranulation and 5-lipoxygenase in human neutrophils, whereas 11 behaved as scavenger of superoxide. Only four compounds (4-7) inhibited cyclo-oxygenase-2 activity. The majority of these samples showed anti-inflammatory effects in the mouse air pouch model.

L92 ANSWER 18 OF 53 MEDLINE
ACCESSION NUMBER: 1998340207 MEDLINE
DOCUMENT NUMBER: 98340207 PubMed ID: 9675607
TITLE: Measurement of cyclooxygenase inhibition in vivo: a study of two non-steroidal anti-inflammatory drugs in sheep.
AUTHOR: Cheng Z; Nolan A M; McKellar Q A
CORPORATE SOURCE: Department of Veterinary Preclinical Studies, University of Glasgow, UK.
SOURCE: INFLAMMATION, (1998 Aug) 22 (4) 353-66.
Journal code: 7600105. ISSN: 0360-3997.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981021
Last Updated on STN: 19981021
Entered Medline: 19981009

AB The anti-inflammatory effects of the non-steroidal anti-inflammatory drugs phenylbutazone (PBZ) and flunixin meglumine (FM) and the relationship between the effects and drug concentration in vivo were studied using a subcutaneous tissue-cage model in sheep. Intracaveal injection of carrageenan induced prostaglandin (PG) E2 production in tissue-cage exudate (maximal concentration, 101 nM) with significant increases in white blood cell (WBC) numbers, skin temperature over the inflamed cage and exudate **leukotriene** B4 (LTB4) concentration ($P < 0.05$). Intravenous PBZ, 4.4 mg kg-1 produced mild inhibition of exudate PGE2 generation (10%), but greater inhibition of serum TXB2 (75.3%). The IC50 for TXB2 was 36.0 microM. Phenylbutazone did not alter effects on skin temperature, WBC numbers or exudate LTB4 concentrations. Intravenous FM, 1.1 mg kg-1, significantly inhibited carrageenan-induced exudate PGE2 formation (Emax, 100%, IC50, < 0.4 nM) and serum TXB2 generation (Emax, 100%, IC50, 17 nM) for up to 32 h. Flunixin meglumine significantly inhibited the rise in skin temperature but had a limited effect on exudate WBC. Phenylbutazone and FM have distinct effects on carrageenan-induced cyclooxygenase (**COX-2**) and platelet COX (COX-1).

Flunixin meglumine was a more potent COX inhibitor than PBZ and was more selective for the inducible form of COX in vivo.

L92 ANSWER 19 OF 53 MEDLINE
ACCESSION NUMBER: 1998319337 MEDLINE
DOCUMENT NUMBER: 98319337 PubMed ID: 9657255
TITLE: Effects of the **cyclooxygenase-2** inhibitor NS-398 on thromboxane and **leukotriene** synthesis in rat peritoneal cells.
AUTHOR: Schuligoi R; Amann R; Prenn C; Peskar B A
CORPORATE SOURCE: Department of Experimental and Clinical Pharmacology, Graz, Austria.. rufina.schuligoi@kfunigraz.ac.at
SOURCE: INFLAMMATION RESEARCH, (1998 May) 47 (5) 227-30. Journal code: 9508160. ISSN: 1023-3830.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980910
Last Updated on STN: 19980910
Entered Medline: 19980903

AB OBJECTIVE: Inhibition of inducible cyclooxygenase (**COX**)-**2** has been suggested to offer therapeutic advantages without some side effects associated with the inhibition of constitutive COX activity. These side effects encompass asthmatic responses that can be induced by analgesic/ antiphlogistic drugs and are possibly related to increased **leukotriene** (LT) biosynthesis. We have therefore investigated whether or not the selective **COX-2** inhibitor NS-398, similar to indomethacin, stimulates **leukotriene** (LT) biosynthesis in rat peritoneal cells. METHODS: Three hours after rats had received intraperitoneal injections of bacterial lipopolysaccharide (LPS) or saline, cells were obtained by peritoneal lavage. Northern blot analysis confirmed induction of **COX-2** mRNA by LPS treatment. For determination of eicosanoid biosynthesis, peritoneal cells were incubated in the presence of various concentrations of test compounds for 60 min. The supernatants were used for radioimmunological determination of immunoreactive eicosanoids. RESULTS: In cells from LPS treated rats, but not in controls, NS-398 (10-300nM) reduced the amount of TXB2-like immunoreactivity (IR) in the supernatants, the maximum effect being a 25% inhibition. At these concentrations, there was no detectable effect of NS-398 on the amount of LTB4-IR or LTC4-IR in the supernatants. At higher concentrations (1-10 microM), NS-398 caused further inhibition of TXB2 synthesis, an effect that was observed also in non-LPS treated preparations. A significant increase of LTB4-IR was caused by 3-10 microM NS-398. Indomethacin (3-100 nM) reduced the amount of TXB2-IR, and at >10 nM increased the amount of LTB4- and LTC4-IR in the supernatant. CONCLUSIONS: The results show that concentrations of NS-398 that selectively inhibited **COX-2** activity, produced no detectable increase in LT biosynthesis, thus raising the possibility that **COX-2** inhibitors are less likely than non-selective COX inhibitors to produce LT- related side effects.

L92 ANSWER 20 OF 53 MEDLINE
ACCESSION NUMBER: 97404293 MEDLINE
DOCUMENT NUMBER: 97404293 PubMed ID: 9262379
TITLE: Evaluation of the antiinflammatory activity of a dual **cyclooxygenase-2** selective/5-lipoxygenase

inhibitor, RWJ 63556, in a canine model of inflammation.
AUTHOR: Kirchner T; Argentieri D C; Barbone A G; Singer M; Steber M; Ansell J; Beers S A; Wachter M P; Wu W; Malloy E; Stewart A; Ritchie D M
CORPORATE SOURCE: The R.W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey 08869, USA.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1997 Aug) 282 (2) 1094-101.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970922
Last Updated on STN: 19970922
Entered Medline: 19970911

AB Sterile perforated polyethylene spheres (wiffle golf balls) were implanted s.c. in beagle dogs. A local inflammatory reaction was elicited within the spheres by injecting carrageenan. Changes in leukocyte count, prostaglandin E2, thromboxane B2 and **leukotriene** B4 levels were monitored in fluid samples collected over a 24-hr period. Blood samples were also collected at various time points and analyzed for prostaglandin E2 and **leukotriene** B4 production after ex vivo calcium ionophore treatment. Effects of standard antiinflammatory agents (aspirin, indomethacin, dexamethasone, tenidap and zileuton) and newer **cyclooxygenase-2** (**COX-2**) selective agents (nimesulide, nabumetone and SC-58125) were determined after oral administration. Ex vivo inhibition of cyclooxygenase product synthesis (prostaglandin E2, thromboxane B2) in whole blood was used as an indicator of activity for the constitutive COX-1 isoform, although inhibition of the synthesis of these mediators in the chamber exudate during an inflammatory process is believed to represent **COX-2** inhibition. Treatment effects on **leukotriene** B4 production were also determined both ex vivo in whole blood and in the fluid. All of the compounds tested, except aspirin, inhibited leukocyte infiltration into the fluid exudate. Inhibitors that exert their effects on both isozymes of cyclooxygenase attenuate production of cyclooxygenase metabolites in both the inflammatory exudate and in peripheral blood ex vivo, although **COX-2** selective inhibitors only demonstrated activity in the exudate. A 5-lipoxygenase inhibitor (zileuton), a corticosteroid (dexamethasone) and a dual **COX-2** selective/5-lipoxygenase inhibitor (RWJ 63556) had similar profiles in that they all inhibited cell infiltration and eicosanoid production in the fluid and also attenuated **leukotriene** B4 production in both the fluid and blood.

L92 ANSWER 21 OF 53 MEDLINE
ACCESSION NUMBER: 96118470 MEDLINE
DOCUMENT NUMBER: 96118470 PubMed ID: 8534265
TITLE: Meloxicam: influence on arachidonic acid metabolism. Part II. In vivo findings.
AUTHOR: Engelhardt G; Bogel R; Schnitzler C; Utzmann R
CORPORATE SOURCE: Department of Pharmacological Research, Dr. Karl Thomae GmbH, Biberach/Riss, Germany.
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1996 Jan 12) 51 (1) 29-38.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 19960220
Last Updated on STN: 19960220
Entered Medline: 19960130

AB Meloxicam is a new nonsteroidal anti-inflammatory drug (NSAID) derived from enolic acid. Preclinical studies have indicated that meloxicam has potent anti-inflammatory activity, together with a good gastrointestinal and renal tolerability profile. This report summarizes studies undertaken to compare meloxicam to other NSAIDs in the inhibition of the inducible cyclooxygenase (**COX-2**) in inflamed areas (pleurisy of the rat, peritonitis of mice) and their influence on the activity of the constitutive cyclooxygenase (COX-1) in stomach, kidney, brain, and blood. In pleurisy of the rat, meloxicam was twice as potent as tenoxicam, 3 times as potent as flurbiprofen, 8 times as potent as diclofenac, and 20 times as potent as tenidap at inhibiting prostaglandin E2 (PGE2) biosynthesis. In the peritonitis model in mice, meloxicam was approximately twice as active as piroxicam, and more than 10 times as active as diclofenac in the suppression of PGE biosynthesis. Doses of meloxicam sufficient to inhibit PGE2 biosynthesis in the pleural exudate and peritoneal exudate had no influence on **leukotriene**-B4 (LTB4) or **leukotriene**-C4 (LTC4) content. The effect of meloxicam on the PGE2 content of rat gastric juice and rat urine was weaker than that of piroxicam or diclofenac. Meloxicam was a weaker inhibitor of the increased PGE2 concentration in brain of rats and mice (induced by convulsant doses of pentetrazole) than piroxicam, diclofenac, or indomethacin. Meloxicam had a weaker effect on serum thromboxane-B2 (TXB2) concentration in rats than piroxicam or tenoxicam. The in vivo findings confirm the results of in vitro tests, conducted separately, showing that meloxicam preferentially inhibits **COX-2** over COX-1. **COX-2** is the inducible isoenzyme implicated in the inflammatory response, whereas COX-1 has cytoprotective effects in the gastric mucosa. Therefore, a preferential selectivity for one isoenzyme over another, as displayed by meloxicam, may have implications in the clinical setting in terms of a more favorable risk: benefit profile.

L92 ANSWER 22 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:695783 HCAPLUS
DOCUMENT NUMBER: 137:216886
TITLE: Preparation of 8-(alkenylaryl)quinoline phosphodiesterase-4 inhibitors
INVENTOR(S): Vailaya, Anant; Conlon, David A.; Ho, Guo-Jie; Macdonald, Dwight; Perrier, Helene; Thibert, Roch; Kwong, Elizabeth; Clas, Sophie-Dorothee
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Merck Frosst Canada & Co.
SOURCE: PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002069970	A1	20020912	WO 2001-US48674	20011214

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002143032 A1 20021003 US 2001-40993 20011109
PRIORITY APPLN. INFO.: US 2000-256803P P 20001220
OTHER SOURCE(S): MARPAT 137:216886

AB Title compds. I [wherein S1-S3 = independently H, OH, halo, NO2, CN, or (un)substituted alkyl or alkoxy; R1 = H, .OH, halo, or (un)substituted acyl, (cyclo)alkyl, alkenyl, alkoxy, (hetero)aryl, heterocycloalkyl, NH2, carbamoyl, sulfamoyl , etc.; A = CH, C-ester, or CR4; R2 and R3 = independently H, halo, CN, CO2H, or (un)substituted (hetero)aryl, (heterocyclo)alkyl, alkoxy, acyl, carbamoyl, etc.; with the proviso that 1 of R2 and R3 must = (hetero)aryl; when R2 and R2 both = (hetero)aryl, then R2 and R3 may be optionally connected by a thio, oxy, or alkyl bridge to from a fused 3-ring system; R4 = CN or (un)substituted (hetero)aryl, alkyl, acyl, carbamoyl, etc.; or R2 or R3 may be optionally joined to R4 by a bond to form a ring; n = 0-2; and pharmaceutically acceptable H2SO4, methanesulfonic acid, p-toluenesulfonic acid, 2-naphthalenesulfonic acid, hydrochloride acid, or benzenesulfonic acid salts thereof] were prepd. as phosphodiesterase-4 (PDE4) inhibitors. For example, a soln. of (E)-1-(3-bromophenyl)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]ethene, diboron pinacol ester, [1,1'-bis(diphenylphosphino)ferrocene]PdCl2, and KOAc in DMF was stirred at 80.degree. for 3 h. Sequential addn. of 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-bromoquinoline, [1,1'-bis(diphenylphosphino)ferrocene]PdCl2, and Na2CO3 followed by heating at 80.degree. overnight gave (E)- and (Z)-II. Forty-two compds. of the invention exhibited IC50 values ranging from 0.04 .mu.M to 8.71 .mu.M in LPS and fMLP-induced TNF-.alpha. and LTB4 assays performed on human whole blood. All but one of same compds. inhibited the hydrolysis of cAMP to AMP by type-IV cAMP-specific phosphodiesterases with IC50 values ranging from 0.14 nM to 10.24 nM. Thus, I are useful as anti-inflammatory and anti-allergic agents for treatment of a wide variety of PDE4-related diseases and conditions (no data).

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 23 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:594822 HCAPLUS
DOCUMENT NUMBER: 137:154857
TITLE: Preparation of nicotinamide biaryl derivatives as inhibitors of PDE4 isozymes
INVENTOR(S): Chambers, Robert James; Magee, Thomas Victor; Marfat, Anthony
PATENT ASSIGNEE(S): Pfizer Productors Inc., USA
SOURCE: PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060875	A1	20020808	WO 2001-IB2341	20011206

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-265492P P 20010131

OTHER SOURCE(S): MARPAT 137:154857

AB The title compds. [I; g = 0-1; j = 0-1; provided that when j = 0, n must be 2; k = 0-1; m = 0-2; n = 1-2; W1 = 0, SOt (t = 0-2), NR3; W2 = OCR9R10, or absent; Y = CR1, NOk (k = 0-1); R9, R10 = H, F, CF3, etc.; or R9 and R10 are taken together, but only in the case where m = 1, to form a spiro moiety; R7, R8 have the same meaning as R9, R10 except that one of them must be H; R1, R2 = H, F, Cl, etc.; R3 = H, alkyl, Ph, etc.; R4-R6 = H, F, Cl, etc.; Q1 = Ph, benzodioxyl, etc.; Q2 = biaryl moiety], useful as inhibitors of PDE4 in the treatment of diseases regulated by the activation and degranulation of eosinophils, esp. asthma, chronic bronchitis, and chronic obstructive pulmonary disease, were prepd. E.g., a multi-step synthesis of the amide II, starting from Me 3-bromobenzoate and 4-formylbenzeneboronic acid, was given. Compds. I showed anti-inflammatory activity at 0.0001 .mu.M to 20.0 .mu.M in whole blood assay for LTE4.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 24 OF 53 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:594628 HCAPLUS

DOCUMENT NUMBER: 137:150265

TITLE: Substituted aryl compounds as novel **cyclooxygenase-2** selective inhibitors, compositions and methods of use

INVENTOR(S): Khanapure, Subhash P.; Garvey, David S.; Earl, Richard A.; Ezawa, Maiko; Fang, Xinqin; Gaston, Ricky D.

PATENT ASSIGNEE(S): Nitromed, Inc., USA

SOURCE: PCT Int. Appl., 132 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060378	A2	20020808	WO 2001-US48823	20011221

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002119977 A1 20020829 US 2001-24046 20011221
PRIORITY APPLN. INFO.: US 2000-256932P P 20001221
OTHER SOURCE(S): MARPAT 137:150265
AB Substituted aryl compds. that are **cyclooxygenase 2** (**COX-2**) selective inhibitors and compns. comprising at least one **COX-2** selective inhibitor, and, optionally, at least one compd. that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or, optionally, at least one therapeutic agent are described. A therapeutic agent is selected from steroids, nonsteroidal anti-inflammatory compds. (NSAID), 5-lipoxygenase (5-LO) inhibitors, **leukotriene** B4 (LTB4) receptor antagonists, **leukotriene** A4 (LTA4) hydrolase inhibitors, 5-HT agonists, 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) inhibitors, H2 antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating antihistaminics, inducible nitric oxide synthase inhibitors, opioids, analgesics, Helicobacter pylori inhibitors, proton pump inhibitors, and isoprostane inhibitors. The invention also provides novel kits comprising at least one **COX-2** selective inhibitor, and, optionally, at least one nitric oxide donor, and/or, optionally, at least one therapeutic agent. The **cyclooxygenase-2** selective inhibitors of the invention can be optionally nitrosated and/or nitrosylated. The invention also provides methods for treating inflammation, pain and fever; for treating and/or improving the gastrointestinal properties of **COX-2** selective inhibitors; for facilitating wound healing; for treating and/or preventing renal toxicity or other toxicities; for treating and/or preventing other disorders resulting from elevated levels of **cyclooxygenase-2**; and for improving the cardiovascular profile of **COX-2** selective inhibitors.

L92 ANSWER 25 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:172487 HCAPLUS
DOCUMENT NUMBER: 136:221745
TITLE: Irrigation solution and method for inhibition of pain and inflammation
INVENTOR(S): Demopulos, Gregory A.; Pierce-Palmer, Pamela; Herz, Jeffrey M.
PATENT ASSIGNEE(S): Omeros Medical Systems, USA
SOURCE: U.S. Pat. Appl. Publ., 58 pp., Cont.-in-part of Appl. No. PCT/US99/24625.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002028798	A1	20020307	US 2001-839633	20010420
WO 9619233	A2	19960627	WO 1995-US16028	19951212
WO 9619233	A3	19960919		

W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK

RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

US 5820583 A 19981013 US 1996-670699 19960626

US 6261279 B1 20010717 US 1998-72913 19980504

WO 2000023061 A2 20000427 WO 1999-US24557 19991020

WO 2000023061 A3 20001116

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

WO 2000023062 A2 20000427 WO 1999-US24558 19991020

WO 2000023062 A3 20000727

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

WO 2000023066 A2 20000427 WO 1999-US24672 19991020

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

WO 2000025745 A2 20000511 WO 1999-US26330 19991105

WO 2000025745 A3 20000824

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 1994-353775 B2 19941212
WO 1995-US16028 A2 19951212
US 1996-670699 A2 19960626
US 1998-72913 A2 19980504
US 1998-105026P P 19981020
US 1998-105029P P 19981020
US 1998-105044P P 19981020
US 1998-105166P P 19981021
US 1998-107256P P 19981105
WO 1999-US24557 A2 19991020

WO 1999-US24558 A2 19991020
WO 1999-US24625 A2 19991020
WO 1999-US24672 A2 19991020
WO 1999-US26330 A2 19991105

AB A method and soln. for perioperatively inhibiting a variety of pain and inflammation processes at wounds from general surgical procedures including oral/dental procedures. The soln. preferably includes at least one pharmacol. agent selected from the group consisting of a mitogen-activated protein kinase (MAPK) inhibitor, an .alpha.2-receptor agonist, a neuronal nicotinic acetylcholine receptor agonist, a **cyclooxygenase-2** (**COX-2**) inhibitor, a sol. receptor and mixts. thereof, and optionally addnl. multiple pain and inflammation inhibitory agents at dil. concn. in a physiol. carrier, such as saline or lactated Ringer's soln. The soln. is applied by continuous irrigation of a wound during a surgical procedure for preemptive inhibition of pain and while avoiding undesirable side effects assocd. with oral, i.m., s.c. or i.v. application of larger doses of the agents.

L92 ANSWER 26 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:84600 HCAPLUS
DOCUMENT NUMBER: 136:151161
TITLE: Preparation of 4-(heterocyclyl)benzenesulfonamides as components of a combination of a **cyclooxygenase-2** inhibitors and a **leukotriene** B4 receptor antagonist
INVENTOR(S): Isakson, Peter C.; Anderson, Gary D.; Gregory, Susan A.
PATENT ASSIGNEE(S): G. D. Searle & Co., USA
SOURCE: U.S., 19 pp., Cont.-in-part of U.S. Ser. No. 489,415, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6342510	B1	20020129	US 1996-661641	19960611
CA 2224563	AA	19961227	CA 1996-2224563	19960611
US 2002107276	A1	20020808	US 2002-38080	20020103

PRIORITY APPLN. INFO.: US 1995-489415 B2 19950612
US 1996-661641 A1 19960611
OTHER SOURCE(S): MARPAT 136:151161

AB The title compds. [I; A = (partially) unsatd. heterocyclyl or carbocyclyl; R1 = (un)substituted heterocyclyl, cycloalkyl, cycloalkenyl, aryl; R2 = Me, NH2; R3 = H, halo, alkyl, etc.] which are **cyclooxygenase-2** inhibitors used in combination with a **leukotriene** B4 receptor antagonists for treatment of inflammation and inflammation-related disorders, were prepd. and formulated. Thus, treating Et trifluoroacetate with NaOMe in Me tert-Bu ether followed by addn. of 4'-chloroacetophenone (85%), and reacting the resulting 4,4,4-trifluoro-1-(4-chlorophenyl)butane-1,3-dione with 4-sulfonamidophenylhydrazine hydrochloride in EtOH afforded 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (80%).

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 27 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:51982 HCAPLUS
DOCUMENT NUMBER: 136:96105
TITLE: Use of **cox-2** inhibitors to treat sepsis, complications thereof, and pros EP receptor modulation
INVENTOR(S): Mack Strong, Vivian E.; Stapleton, Philip P.; Daly, John M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 39 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002006915	A1	20020117	US 2001-782936	20010214

PRIORITY APPLN. INFO.: US 2000-182524P P 20000215
AB The present invention is directed to methods of preventing, inhibiting, reversing and/or ameliorating complications in those having or at risk for systemic inflammatory response syndrome, e.g., sepsis, including multiple organ dysfunction syndrome, pancreatitis, burns, trauma, and complications of sepsis such as bacteremia, pneumonia, urinary tract infections, wound infections, and drug reactions. The methods comprise administration of an effective amt. of at least one of a selective inhibitor of **cyclooxygenase-2**, a drug which stimulates one or more PGE2 receptors or a drug which interferes with binding of PGE2 to one of more PGE2 receptors.

L92 ANSWER 28 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:5125 HCAPLUS
DOCUMENT NUMBER: 136:319026
TITLE: A pyrroloquinazoline derivative with anti-inflammatory and analgesic activity by dual inhibition of cyclo-oxygenase-2 and 5-lipoxygenase
AUTHOR(S): Rioja, Inmaculada; Terencio, M. Carmen; Ubeda, Amalia; Molina, Pedro; Tarraga, Alberto; Gonzalez-Tejero, Antonia; Alcaraz, M. Jose
CORPORATE SOURCE: Facultad de Farmacia, Departamento de Farmacologia, Universidad de Valencia, Burjasot, Valencia, 46100, Spain
SOURCE: European Journal of Pharmacology (2002), 434(3), 177-185
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In a previous study, we reported a new pyrroloquinazoline deriv., 3-(4'-acetoxy-3',5'-dimethoxy)benzylidene-1,2-dihydropyrrolo[2,1-b]quinazoline-9-one (PQ), which inhibited human purified 5-lipoxygenase activity and prostaglandin E2 release in lipopolysaccharide-stimulated RAW 264.7 cells. In the present work, we show that PQ inhibits cyclo-oxygenase-2 activity in intact cell assays (human monocytes) and purified enzyme prepns. (ovine isoenzymes) without affecting

cyclo-oxygenase-1 activity. This behavior was confirmed in vivo by using the zymosan-injected mouse air pouch model, where PQ caused a marked redn. in cell migration and **leukotriene** B4 levels at 4 h, as well as inhibition of prostaglandin E2 levels without affecting cyclo-oxygenase-2 expression at 24 h after zymosan stimulation. In addn., oral administration of this compd. significantly reduced carrageenan-induced mouse paw edema and phenyl-p-benzoquinone-induced writhings in mice. These results indicate that oral PQ exerts analgesic and anti-inflammatory effects, which are related to dual inhibition of cyclo-oxygenase-2 and 5-lipoxygenase activities.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 29 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:811166 HCAPLUS
DOCUMENT NUMBER: 136:161131
TITLE: Acute effects of the cys-**leukotriene**-1 receptor antagonist, montelukast, on experimental colitis in rats
AUTHOR(S): Holma, Reetta; Salmenpera, Pertteli; Riutta, Asko; Virtanen, Ismo; Korpela, Riitta; Vapaatalo, Heikki
CORPORATE SOURCE: Institute of Biomedicine, Pharmacology, Biomedicum Helsinki, University of Helsinki, Helsinki, FIN-00014, Finland
SOURCE: European Journal of Pharmacology (2001), 429(1-3), 309-318
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cysteinyl **leukotrienes** play a part in inflammatory reactions such as inflammatory bowel diseases. The aim of the present study was to evaluate the acute effects of a cys-**leukotriene**-1 receptor antagonist, montelukast, on trinitrobenzene sulfonic acid (TNBS)-induced colitis in rats. Montelukast (5, 10 or 20 mg kg-1 day-1), a 5-lipoxygenase inhibitor, zileuton (50 or 100 mg kg-1 day-1, a pos. control), or the vehicle was administered intracolonically to the rats twice daily throughout the study, starting 12 h before the induction of colitis with TNBS. The severity of colitis (macroscopic and histol. assessment, as well as myeloperoxidase activity), the protein expression of inducible nitric oxide synthase (iNOS) and **cyclooxygenase-2**, and eicosanoid prodn. in colonic tissue incubation were assessed 24 and 72 h after colitis induction. Montelukast increased prostaglandin E2 prodn. at 24 h and tended to reduce the **cyclooxygenase-2** protein expression at 72 h, but did not influence the severity of colitis. Zileuton failed to decrease the inflammatory reaction in spite of reduced **leukotriene** B4 prodn. at 72 h. The results suggest that drugs that block cysteinyl **leukotriene** receptors have limited potential to ameliorate acute TNBS-induced colitis, but that they exert some beneficial effects which make them capable of modulating the course of colitis.

REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 30 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:795108 HCAPLUS
DOCUMENT NUMBER: 136:144877
TITLE: Identification of Dual Cyclooxygenase-Eicosanoid

Oxidoreductase Inhibitors: NSAIDs That Inhibit PG-LX Reductase/LTB4 Dehydrogenase
AUTHOR(S): Clish, Clary B.; Sun, Yee-Ping; Serhan, Charles N.
CORPORATE SOURCE: Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Biochemical and Biophysical Research Communications (2001), 288(4), 868-874
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Eicosanoids play key roles in many physiol. and disease processes, and their regulation by nonsteroidal anti-inflammatory drugs (NSAIDs) is crit. to many therapeutic approaches. These autacoids are rapidly inactivated by specific enzymes such as 15-hydroxyprostaglandin dehydrogenase (15-PGDH) and 15-oxoprostaglandin 13-reductase/**leukotriene** B4 12-hydroxydehydrogenase (PGR/LTB4DH) that act on main series of eicosanoids (i.e., **leukotrienes**, prostaglandins), and recently found to act in lipoxin inactivation. Here, a panel of NSAIDs was assessed to det. each compd.'s ability to inhibit eicosanoid-directed activities of either the recombinant 15-PGDH or the PG-LXR/LTB4DH. The recombinant 15-PGDH that acts on both prostaglandin E2 (PGE2) and lipoxin A4 (LXA4) was not significantly inhibited by the NSAIDs tested. In contrast, several of the widely used NSAIDs were potent inhibitors of the PG-LXR/LTB4DH that metabolizes 15-oxo-PGE2, and LTB4 as well as 15-oxo-LXA4. Diclofenac and indomethacin each inhibited PG-LXR/LTB4DH-catalyzed conversion of 15-oxo-PGE2 to 13,14-dihydro-15-oxo-PGE2 by 70 and 95%, resp. Also, a **COX-2** inhibitor, niflumic acid, inhibited the PG-LXR/LTB4DH eicosanoid oxidoreductase (EOR) by 80% while other **COX-2** inhibitors such as nimesulide and NS-398 did not inhibit this enzyme. These results indicate that certain clin. useful NSAIDs such as diclofenac and indomethacin, in addn. to inhibiting cyclooxygenases (1 and 2), also interfere with eicosanoid degrdn. by blocking PG-LXR/LTB4DH (EOR) and are members of a new class of dual cyclooxygenase (COX)-EOR inhibitors. Moreover, they suggest that the impact of NSAIDs on PG-LXR/LTB4DH activities as targets in the local tissue regulation of eicosanoid-mediated processes should be taken into account. (c) 2001 Academic Press.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 31 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:472677 HCAPLUS
DOCUMENT NUMBER: 135:76803
TITLE: Synthesis and use of substituted 8-arylquinolines (and sulfonic acid salts thereof) as inhibitors of phosphodiesterase-4
INVENTOR(S): Deschenes, Denis; Dube, Daniel; Gallant, Michel; Girard, Yves; Lacombe, Patrick; MacDonald, Dwight; Mastracchio, Anthony; Perrier, Helene
PATENT ASSIGNEE(S): Merck Frosst Canada + Co., Can.
SOURCE: PCT Int. Appl., 263 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001046151	A1	20010628	WO 2000-CA1559	20001220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6410563	B1	20020625	US 2000-741517	20001220
US 2002103226	A1	20020801		
BR 2000016651	A	20020910	BR 2000-16651	20001220
EP 1244628	A1	20021002	EP 2000-986937	20001220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
NO 2002003013	A	20020822	NO 2002-3013	20020621

PRIORITY APPLN. INFO.:	US 1999-171522P	P	19991222
	WO 2000-CA1559	W	20001220

OTHER SOURCE(S): MARPAT 135:76803

AB Compds. of formula I are claimed [wherein; S1-3 = H, OH, halo, (substituted)alkyl/alkoxy, NO2 and CN; R1 = H, OH, halo, CO, (cyclo)alkyl, alkenyl, alkoxy, (hetero)aryl, CN, etc.; R2-3 = H, alkyl, halo, heterocycloalkyl, alkoxy, CO, carbamoyl, COOH, alkyl-S(O)0-2-alkyl; etc.; one of R2 or R3 must be (substituted) aryl/heteroaryl and when both R2 and R3 are aryl/heteroaryl then R2 and R3 may be optionally connected by a S, O or alkyl bridge to form a fused three ring system; A = CH, C-ester or CR4 where R4 = aryl, alkyl, heteroaryl, CN, CO, etc.; R2 or R3 may also be joined to R4 by a bond to form a ring]. Over 40 synthetic examples are given. For instance, 4-(methylsulfonyl)phenylacetic acid was condensed with acetamide oxime to give (3-methyl-1,2,4-oxadiazol-5-yl)[4-(methylsulfonyl)phenyl]methane. This intermediate was condensed with 3-bromobenzaldehyde to give the (E)-bromide. Pd-mediated coupling of the (E)-bromide, via the intermediate pinacol boronate deriv. (not isolated), to the substituted 8-bromoquinoline furnished biaryl II. Several sulfonic acid salts of II as well as 2 polymorphs of the benzenesulfonic acid salt of II were characterized (NMR, XRPD, etc.). In an assay of LPS and fMLP-induced TNF-.alpha. and LTB4 prodn. in whole blood (surrogate markers for PDE-4 inhibition), example compds. had IC50 = 0.04 to 8.71 .mu.M. Compds. of the invention also inhibited a type-IV cAMP-specific PDE, IC50 = 0.14 to 10.24 nM. A method to treat/prevent asthma, chronic bronchitis, chronic obstructive pulmonary disease, eosinophilic granuloma, psoriasis, etc. is a claimed use of the invention.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 32 OF 53 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:207649 HCAPLUS

DOCUMENT NUMBER: 135:40643

TITLE: Dysidotronic acid, a new sesquiterpenoid, inhibits cytokine production and the expression of nitric oxide synthase

AUTHOR(S): Posadas, I.; Terencio, M. C.; Giannini, C.; D'Auria, M. V.; Paya, M.

CORPORATE SOURCE: Departamento de Farmacologia, Facultad de Farmacia, Universidad de Valencia, Burjassot, Valencia, 46100, Spain
SOURCE: European Journal of Pharmacology (2001), 415(2,3), 285-292
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In a previous study, we reported a new bioactive sesquiterpenoid, named dysidotronic acid, to be a potent, selective human synovial phospholipase A2 inhibitor. Dysidotronic acid is a novel, non-complex manoalide analog lacking the pyranofuranone ring. We now investigate the effect of this compd. on cytokine, nitric oxide and prostanoid generation on the mouse macrophage cell line RAW 264.7, where it showed a dose-dependent inhibition with inhibitory concn. 50% values in the micromolar range. This effect was also confirmed in the mouse air pouch injected with zymosan. Dysidotronic acid inhibited the prodn. of tumor necrosis factor alpha and interleukin-1 beta as well as the prodn. of nitric oxide, prostaglandin E2 and **leukotriene** B4. Decreased nitric oxide generation was the consequence of inhibition of the expression of nitric oxide synthase, whereas PGE2 and LTB4 redn. was due to inhibition of arachidonic acid bioavailability through a direct inhibitory effect of dysidotronic acid on secretory phospholipase A2.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L92 ANSWER 33 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:557660 HCAPLUS
DOCUMENT NUMBER: 127:239120
TITLE: Compositions comprising a **cyclooxygenase-2** inhibitor and a **leukotriene** B4 receptor antagonist for reducing transplant rejection
INVENTOR(S): Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
PATENT ASSIGNEE(S): G.D. Searle & Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9729775	A1	19970821	WO 1997-US1422	19970211
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2246356	AA	19970821	CA 1997-2246356	19970211
AU 9722500	A1	19970902	AU 1997-22500	19970211
EP 880362	A1	19981202	EP 1997-905663	19970211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				

JP 2000505445	T2	20000509	JP 1997-529359		19970211
US 6172096	B1	20010109	US 1998-75633		19980511
PRIORITY APPLN. INFO.:			US 1996-600580	A1	19960213
			WO 1997-US1422	W	19970211

OTHER SOURCE(S): MARPAT 127:239120

AB Treatment with a **cyclooxygenase-2** inhibitor and a **leukotriene** B4 receptor antagonist is described as being useful in reducing recipient rejection of transplanted organs and for treatment of autoimmune diseases.

L92 ANSWER 34 OF 53 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:175052 HCAPLUS
DOCUMENT NUMBER: 126:166481
TITLE: Combination of a **cyclooxygenase-2** inhibitor and a **leukotriene** B4 receptor antagonist for the treatment of inflammations
INVENTOR(S): Isakson, Peter C.; Anderson, Gary D.; Gregory, Susan A.
PATENT ASSIGNEE(S): G.D. Searle & Co., USA
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9641645	A1	19961227	WO 1996-US9905	19960611
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
CA 2224563	AA	19961227	CA 1996-2224563	19960611
AU 9662694	A1	19970109	AU 1996-62694	19960611
EP 833664	A1	19980408	EP 1996-921477	19960611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 11507669	T2	19990706	JP 1996-503237	19960611
PRIORITY APPLN. INFO.:			US 1995-489415 A	19950612
			WO 1996-US9905 W	19960611

OTHER SOURCE(S): MARPAT 126:166481

AB Combinations of a **cyclooxygenase-2** inhibitor and a **leukotriene** B4 receptor antagonist are described for treatment of inflammation and inflammation-related disorders. The **cyclooxygenase-2** inhibitors were prepd. Also, formulations for the drug combination are described.

L92 ANSWER 35 OF 53 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-22912 DRUGU P B
TITLE: **Ebselen**, a glutathione peroxidase mimetic seleno-organic compound, as a multifunctional antioxidant.
AUTHOR: Nakamura Y; Feng Q; Kumagai T; Torikai K; Ohigashi H; Osawa T; Noguchi N; Niki E; Uchida K
CORPORATE SOURCE: Univ.Nagoya; Univ.Kyoto; Univ.Tokyo
LOCATION: Nagoya, Kyoto; Tokyo, Jap.
SOURCE: J.Biol.Chem. (277, No. 4, 2687-94, 2002) 7 Fig. 65 Ref.

CODEN: JBCHA3 ISSN: 0021-9258
AVAIL. OF DOC.: Laboratory of Food and Biodynamics, Nagoya University Graduate School of Bioagricultural Sciences, Nagoya 464-8601, Japan. (K.U.). (e-mail: uchidak@agr.nagoya-u.ac.jp).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Topical **ebselen** (Daiichi) pretreatment inhibited 12-O-tetradecanylphorbol-13-acetate (TPA)-induced increase in thiobarbituric acid-reacting substances (TBARS) level in a mouse skin model. **Ebselen** suppressed hydrogen peroxide (H2O2) formation, TPA-induced skin edema formation and infiltration of PMN, and **COX-2** protein expression. **Ebselen** also inhibited O2 generation. In vitro, **ebselen** induced NAD(P)H:(quinone-acceptor)oxidoreductase (NQO1) activity and glutathione S-transferase (GST) activity and increased GSTP1 and chloramphenicol acetyltransferase (ECAT) gene in rat hepatocyte RL34 cells. Data suggest that **ebselen** is a potential chemopreventive agent in inflammation-associated carcinogenesis.

L92 ANSWER 36 OF 53 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-20358 DRUGU P B S
TITLE: The mechanism of action of the new antiinflammatory compound ML3000: inhibition of 5-LOX and COX-1/2.
AUTHOR: Tries S; Neupert W; Laufer S
CORPORATE SOURCE: Merckle; Univ.Tubingen
LOCATION: Blaubeuren; Tubingen, Ger.
SOURCE: Inflammation Res. (51, No. 3, 135-43, 2002) 8 Fig. 77 Ref.
CODEN: INREF ISSN: 1023-3830
AVAIL. OF DOC.: Preclinical Development, Merckle GmbH, P.O. Box 1161, DE-89135 Blaubeuren, Germany. (e-mail: susatrie@merckle.de).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB In human whole blood, ML-3000 (Merckle) blocked TXB2 production without increasing LTC4 production. ML-3000 blocked LTB4 production in RBL cells. In rats with carrageenan-induced paw edema, p.o. ML-3000 suppressed PGE2 and LTB4 production in the inflamed paw. In rats with trinitrobenzenesulfonic acid (TNBS, Caledon) colitis, p.o. ML-3000 suppressed both colon LTB4 and PGE2 production without altering stomach LTB4 production, using indomethacin (Sigma-Chem.), **MK-886** (Merck-Frosst), nordihydroguaiaretic acid (NDGA) and diclofenac as standard. GI tolerability of ML-3000 reflected its combined inhibition of cyclooxygenase-1 (COX-1), **COX-2**, and 5-lipoxygenase.

L92 ANSWER 37 OF 53 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-03139 DRUGU P B E
TITLE: Effects of **MK-886** and L-745,337 on growth and apoptosis in HT-29 colon cancer cells.
AUTHOR: Lazzeri G; Blandizzi C; Fulceri F; Danesi R; Del Tacca M
CORPORATE SOURCE: Univ.Pisa
LOCATION: Pisa, It.
SOURCE: Biomed.Pharmacother. (54, No. 8-9, 470, 2000)
CODEN: BIPHEX ISSN: 0753-3322
AVAIL. OF DOC.: Division of Pharmacology, Department of Oncology, Transplants

and Advanced Technologies in Medicine, University of Pisa, Pisa, Italy.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB In-vitro effects of **MK-886** and L-745337 on proliferation and apoptosis of HT29-cells were investigated. 5-Lipoxygenase and cyclooxygenase pathways may have differential roles here. (conference abstract: 6th International Congress on Advances in Management of Malignancies, Pisa, Italy, 2000).

L92 ANSWER 38 OF 53 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 2000-23856 DRUGU P E
TITLE: Inhibition of TNF-alpha induced NF-kappa-B activation by inhibitors of the arachidonate cascade.
AUTHOR: Gilston V; Winyard P G
LOCATION: London, U.K.
SOURCE: Rheumatol. (39, Abstr. Suppl., 3, 2000) ISSN: 1462-0324
AVAIL. OF DOC.: Bone and Joint Research Unit, St. Bartholomew's and the Royal London School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ, England. (P.G.W.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB In-vitro exposure to **NS-398** or **MK-886** prevented activation of transcription factor NF-kappa-B by tumor necrosis factor-alpha (TNF-alpha) in Jurkat-cells. Inhibitors of other reactive oxygen intermediate-generating enzymes failed to prevent NF-kappa-B activation here. **Cyclooxygenase-2** (**COX-2**) and 5-lipoxygenase (5-LO) may have an important role in TNF-alpha-induced NF-kappa-B activation. (conference abstract: British Society for Rheumatology XVIIth Annual General Meeting and the British Health Professionals in Rheumatology Spring Meeting, Brighton, U.K., 2000).

L92 ANSWER 39 OF 53 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1999-24135 DRUGU P E
TITLE: Relationship of arachidonic acid metabolizing enzyme expression in epithelial cancer cell lines to the growth effect of selective biochemical inhibitors.
AUTHOR: Hong S H; Avis I; Vos M D; Martinez A; Treston A M; Mulshine J L
CORPORATE SOURCE: Nat.Cancer-Inst.Bethesda
LOCATION: Bethesda, Md., USA
SOURCE: Cancer Res. (59, No. 9, 2223-28, 1999) 3 Fig. 3 Tab. 36 Ref. CODEN: CNREA8 ISSN: 0008-5472
AVAIL. OF DOC.: Cell and Cancer Biology Depart., Medicine Branch, National Cancer Institute, Building 10/12N226, 9000 Rockville Pike, Bethesda, MD 20892-1906, U.S.A. (J.L.M.). (e- mail: mulshinej@bprb.nci.nih.gov).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The relationship between enzyme expression status and growth inhibition

by the biochemical inhibitors, AA-861 (docebenone), **MK-886**, baicalein, CDC, NDGA (nordihydroguaiaretate), ETYA (eicosatetraynoate; RO-3-1428), aspirin, **NS-398** (all Biomol) and indomethacin was evaluated in 4 cancer cell lines with defined expression status for 12-LOX, 15-LOX and **COX-2** ; SKBR3, ZR75, T47D and COLO205. LOX inhibitors showed high growth inhibition, whereas COX inhibitors (aspirin and **NS-398**) showed little effect on growth. The degree of inhibition was not correlated with the expression status of the enzymes. Results demonstrate that mRNA expression status for arachidonic metabolizing enzymes does not reliably predict the level of growth inhibition by defined arachidonic acid metabolism inhibitors.

L92 ANSWER 40 OF 53 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1999-00392 DRUGU P E
TITLE: Modulation by lipid mediators of immune complex-induced lung inflammation in mice.
AUTHOR: Steil A A; Tavares de Lima W; Jancar S
CORPORATE SOURCE: Univ.Vale-do-Itajai; Univ.Sao-Paulo
LOCATION: Santa Catarina; Sao Paulo, Braz.
SOURCE: Eur.J.Pharmacol. (361, No. 1, 93-99, 1998) 3 Fig. 1 Tab. 33 Ref.
CODEN: EJPHAZ ISSN: 0014-2999
AVAIL. OF DOC.: Department of Immunology, Institute of Biomedical Sciences, University of Sao Paulo, Av. Prof. Lineu Prestes 2415, 05508-900 Sao Paulo, SP, Brazil. (S.J.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The present study characterized a murine model of immune complex-induced pneumonitis and investigated the role of PAF and eicosanoids as mediators of lung neutrophil infiltration and hemorrhagic lesions, using the antagonists: i.v. WEB-2170 (Boehr.Ingelheim), i.v. indometacin (IND; Sigma-Chem.), p.o. **MK-886** (Merck-Frosst) and p.o. RO-0254094 (Roche). It was demonstrated that neutrophil infiltration and vascular lesions in this Arthus reaction model of immune complex-induced pneumonitis in mice are mediated by LTB4.

L92 ANSWER 41 OF 53 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1999-00185 DRUGU P E
TITLE: Inhibitors of lipoxygenase: a new class of cancer chemopreventive agents.
AUTHOR: Rioux N; Castonguay A
CORPORATE SOURCE: Univ.Laval
LOCATION: Quebec City, Que., Can.
SOURCE: Carcinogenesis(London) (19, No. 8, 1393-400, 1998) 3 Fig. 4 Tab. 49 Ref.
CODEN: CRNGDP ISSN: 0143-3334
AVAIL. OF DOC.: Laboratory of Cancer Etiology, Faculty of Pharmacy, laval University, Quebec City, Canada G1K 7P4. (A.C.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Chronic dietary A-79175 (Abbott), **MK-886** (Merck-Frosst), aspirin (ASA, Sigma-Chem.) and ASA + A-79175 inhibited the multiplicity of p.o. NK (4-(methylnitrosamino)- 1-(3-pyridyl)-1-

butanone, Chemsyn)-induced lung tumors in mice, with the combination of ASA and A-79175 being the most effective. **MK-886** and A-79175 were more effective than ASA at decreasing the proliferation of 82-132 and LM2 murine lung tumor cells. Following exposure to soybean lipoxygenases +/- murine lung microsomal proteins, activation NNK by alpha-carbon hydroxylation was inhibited by arachidonate and A-79175. The results suggest that inhibitor of 5-lipoxygenase may be useful agents for preventing the development of lung tumors.

L92 ANSWER 42 OF 53 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1998-38128 DRUGU P
TITLE: **Inhibition** of **COX-2** and induction of apoptosis: two determinants of NSAIDs chemopreventive efficacies in mouse lung tumorigenesis.
AUTHOR: Yao R; Rioux N; Castonguay A; You M
CORPORATE SOURCE: Med.Coll.Ohio; Univ.Laval
LOCATION: Toledo, Ohio, USA; Quebec City, Que., Can.
SOURCE: Proc.Am.Assoc.Cancer Res. (39, 89 Meet., 195, 1998) ISSN: 0197-016X
AVAIL. OF DOC.: Department of Pathology, Medical College of Ohio, Toledo, OH 43609, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Acetysalicyclate, paracetamol and **NS-398** reduced the number of lung multiplicities, increased the apoptotic index and significantly **inhibited** the expression of **COX-2** in mice treated with the carcinogen 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). These results suggest lung tumor prevention involved both the induction of apoptosis and the inhibition of prostaglandin synthesis. (conference abstract).

L92 ANSWER 43 OF 53 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1998-15439 DRUGU T
TITLE: Enzyme-inhibitors as drugs. (Part III).
AUTHOR: Nuhn P
CORPORATE SOURCE: Univ.Martin-Luther
LOCATION: Halle, Ger.
SOURCE: Pharm.Unserer Zeit (27, No. 1, 12-17, 1998) 33 Ref. CODEN: PHUZBI ISSN: 0048-3664
AVAIL. OF DOC.: Fachbereich Pharmazie, Martin-Luther-Universitaet Halle-Wittenberg, Wolfgang-Langenbeck-Str. 4, 06120 Halle, Germany.
LANGUAGE: German
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The use of enzyme-inhibitors as drugs is reviewed with reference to inhibitors of the biosynthesis of mediators of inflammation, protease inhibitors, inhibitors of enzymes involved in carbohydrate and fat metabolism, and inhibitors of carbonic anhydrase. Protease inhibitors are used in treatment of coagulation disorders, hemorrhagic shock, septic shock, inflammatory diseases (pancreatitis, rheumatoid arthritis, acute respiratory syndrome, lung emphysema) and ulceration of the cornea. Inhibitors of carbohydrate metabolism can be used in combination with insulin to prevent accumulation of sorbitol and fructose. Inhibitors of carbonic anhydrase are used as diuretics and antiepileptics, and in

treatment of glaucoma.

L92 ANSWER 44 OF 53 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1996-23186 DRUGU P B E
TITLE: New pharmacological strategies for pain relief.
AUTHOR: Dray A; Urban L
CORPORATE SOURCE: Sandoz
LOCATION: London, U.K.
SOURCE: Annu.Rev.Pharmacol.Toxicol. (36, 253-80, 1996) 4 Fig. 193 Ref.
CODEN: ARPTDI ISSN: 0362-1642
AVAIL. OF DOC.: Astra Pain Research Unit, 275 boul. Armand Frappier, Laval, Quebec, Canada H7V 4A7.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB New pharmacological strategies for pain relief are reviewed. New targets for analgesic drug development include inhibition of inflammatory mediators (kinins, growth factors), newly expressed proteins (B1 receptors, **COX-2**) and blockers of afferent fiber activity (capsaicin analogs, ion channel blockers). In the CNS more strategies can be pursued, including development of antagonists of specific neuropeptide and glutamate receptors or agonists for purine and amine receptors. Such drugs will inevitably supplement or replace conventional NSAID and opioid analgesics. Further characterization of gene regulation will allow the development of drugs that genetically modify cellular activity altered by chronic pain.

L92 ANSWER 45 OF 53 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002172169 EMBASE
TITLE: New trends in dual 5-LOX/COX inhibition.
AUTHOR: de Leval X.; Julemont F.; Delarge J.; Pirotte B.; Dogne J.-M.
CORPORATE SOURCE: X. de Leval, University of Liege, Department of Medicinal Chemistry, 1 avenue de l'Hopital, B-4000 Liege, Belgium. xdeleval@ulg.ac.be
SOURCE: Current Medicinal Chemistry, (2002) 9/9 (941-962). Refs: 214
ISSN: 0929-8673 CODEN: CMCHE7
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Dual inhibitors are drugs able to block both the COX and the 5-LOX metabolic pathways. The interest of developing such compounds is supported by a large number of pharmacological studies. Compared to COX or LOX pathways single inhibitors, dual inhibitors present at least two major advantages. First, dual inhibitors, by acting on the two major arachidonic acid metabolic pathways, possess a wide range of anti-inflammatory activity. Secondly, dual inhibitors appear to be almost exempt from gastric toxicity, which is the most troublesome side effect of COX inhibitors. The mechanism of their gastric-sparing properties is not completely understood, although it has been demonstrated that

leukotrienes significantly contribute to the gastric epithelial injury. Finally, both COX and LOX derivatives (prostanoids and **leukotrienes**, respectively) are involved in other diseases than inflammation such as cancer proliferation where the use of dual inhibitors could be an interesting approach.

L92 ANSWER 46 OF 53 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001392265 EMBASE
TITLE: Future advances in COPD therapy.
AUTHOR: Barnes P.J.
CORPORATE SOURCE: Prof. P.J. Barnes, National Heart and Lung Institute, Imperial College School of Medicine, Dovehouse St, London SW3 6LY, United Kingdom. p.j.barnes@ic.ac.uk
SOURCE: Respiration, (2001) 68/5 (441-448).
Refs: 67
ISSN: 0025-7931 CODEN: RESPBD
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB There is a pressing need for more effective drug treatments for COPD. New bronchodilators include a long-acting anticholinergic tiotropium bromide and a dual .beta.(2)-dopamine(2-)receptor agonist. But no treatments prevent the progression of COPD. Mediator antagonists in development include **leukotriene** B(4) antagonists, chemokine receptor antagonists and more potent antioxidants. The inflammation of COPD is resistant to corticosteroids, so new anti-inflammatory drugs need to be developed. These include phosphodiesterase-4 inhibitors, nuclear factor-.kappa.B inhibitors and p38 MAP kinase inhibitors. Small molecule protease inhibitors, including neutrophil elastase inhibitors and selective matrix metalloproteinase inhibitors are also in development. Future drug targets may be identified by gene array and proteomics. Copyright.COPYRGT. 2001 S. Karger AG, Basel.

L92 ANSWER 47 OF 53 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001044744 EMBASE
TITLE: Platelet-activating factor, eicosanoids, and bradykinin as targets for adjuvant therapies for sepsis.
AUTHOR: Fink M.P.
CORPORATE SOURCE: Dr. M.P. Fink, Critical Care Medicine Division, Univ. of Pittsburgh Medical School, Scaife Hall, 3550 Terrace, Pittsburgh, PA 15261, United States
SOURCE: Seminars in Pediatric Infectious Diseases, (2001) 12/1 (30-41).
Refs: 218
ISSN: 1045-1870 CODEN: SPIDFJ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

SUMMARY LANGUAGE: English
AB The term "autocoid" has been used to denote a diverse group of relatively small molecules that are released by cells and function as autocrine or paracrine hormones. Many autocoids, including thromboxane A(2), various **leukotrienes**, platelet-activating factor, and bradykinin, are released as part of the inflammatory response and have been implicated in the pathogenesis of sepsis and septic shock. In numerous animal models of sepsis or septic shock, survival, systemic hemodynamics, or organ system function have been improved by administering pharmacologic agents to block the formation of, or the cellular receptors for, various autocoids. Unfortunately, clinical trials of drugs to block prostaglandin formation or the receptors for platelet-activating factor or bradykinin have yielded disappointing results. As a consequence, enthusiasm for this approach for the treatment of sepsis has waned. Copyright .COPYRGT. 2001 by W.B. Saunders Company.

L92 ANSWER 48 OF 53 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97206333 EMBASE
DOCUMENT NUMBER: 1997206333
TITLE: Combination of a **cyclooxygenase-2** inhibitor with a **leukotriene** B.
AUTHOR: Searle G.D.
CORPORATE SOURCE: . pn29@student.open.ac.uk
SOURCE: Expert Opinion on Therapeutic Patents, (1997) 7/7 (765-766).
Refs: 12
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB This patent describes administration of several fixed combination of a selective **cyclooxygenase-2** inhibitor with a **leukotriene** B4 receptor antagonist for the treatment of inflammatory diseases.

L92 ANSWER 49 OF 53 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95309637 EMBASE
DOCUMENT NUMBER: 1995309637
TITLE: Recent developments with investigational drugs potentially useful in the treatment of allergic and inflammatory disorders.
AUTHOR: Carruthers N.I.; Kaminski J.J.
CORPORATE SOURCE: Schering-Plough Research Institute, 2015 Galloping Hill Road,Kenilworth, NJ 07033, United States
SOURCE: Expert Opinion on Investigational Drugs, (1995) 4/10 (1021-1025).
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
031 Arthritis and Rheumatism

030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Investigational drugs that either inhibit the metabolism of arachidonic acid to prostaglandins and **leukotrienes**, or antagonise **leukotriene** receptors, continue to be evaluated clinically. The encouraging clinical results observed with these agents provide the best opportunity to realise novel chemical entities, which operate by specific and unique mechanisms of action, that are also potentially useful therapeutics for the treatment of allergic and inflammatory disorders. Recently, a commentary on new drugs for asthma and a report describing progress with investigational drugs for treating pulmonary and inflammatory diseases have been published. In addition, the discovery of an 'inducible' form of cyclooxygenase, **COX-2**, has also stimulated a resurgence of interest to discover selective inhibitors of this enzyme. The intent of this monthly update is to report the current status of investigational drugs that have been described previously, as well as to introduce novel chemical entities that have entered various stages of preclinical and clinical development.

L92 ANSWER 50 OF 53 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95297857 EMBASE
DOCUMENT NUMBER: 1995297857
TITLE: Pharmacology in Europe.
AUTHOR: Parnham M.J.
CORPORATE SOURCE: Parnham Advisory Services, Von-Guericke-Allee 4,D-53125 Bonn, Germany
SOURCE: Drug News and Perspectives, (1995) 8/6 (352-358).
ISSN: 0214-0934 CODEN: DNPEED
COUNTRY: Spain
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
022 Human Genetics
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

L92 ANSWER 51 OF 53 WPIX (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-666669 [71] WPIX
CROSS REFERENCE: 1997-065309 [06]; 2002-279332 [32]
DOC. NO. CPI: C2002-187040
TITLE: New combination of a **cyclooxygenase-2 inhibitor** and a **leukotriene B4** receptor **antagonist**, useful for treating inflammatory disorders, especially arthritis.
DERWENT CLASS: B05
INVENTOR(S): ANDERSON, G D; GREGORY, S A; ISAKSON, P C
PATENT ASSIGNEE(S): (PHAA) PHARMACIA CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO KIND DATE WEEK LA PG

US 2002107276 A1 20020808 (200271)*		20

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002107276 A1	CIP of	US 1995-489415	19950612
	Cont of	US 1996-661641	19960611
		US 2002-38080	20020103

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 2002107276 A1	Cont of	US 6342510

PRIORITY APPLN. INFO: US 1996-661641 19960611; US 1995-489415 19950612; US 2002-38080 20020103

AB US2002107276 A UPAB: 20021105
NOVELTY - Combination of a **cyclooxygenase-2 inhibitor** (I) and a **leukotriene B4** receptor **antagonist** (II) is new.
ACTIVITY - Antiinflammatory; antiarthritic.
Test details are described but no results given.
MECHANISM OF ACTION - **Cyclooxygenase-2 inhibitor; leukotriene B4** receptor **antagonist.**
USE - The combination is useful for treating inflammatory disorders, especially arthritis.
Dwg.0/0

L92 ANSWER 52 OF 53 WPIX (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-638839 [73] WPIX
DOC. NO. CPI: C2001-188896
TITLE: New nicotinamide benzofused-heterocyclyl derivatives, useful for the treatment of e.g. seasonal allergic rhinitis, arthritis and gout, are selective inhibitors of PDE4 isozymes.
DERWENT CLASS: B02
INVENTOR(S): CHAMBER, R J; MARFAT, A
PATENT ASSIGNEE(S): (PFIZ) PFIZER PROD INC
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001057036 A1		20010809	(200173)*	EN	196

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001027002 A	20010814	(200173)	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001057036 A1		WO 2001-IB124	20010130
AU 2001027002 A		AU 2001-27002	20010130

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001027002 A	Based on	WO 200157036

PRIORITY APPLN. INFO: US 2000-179284P 20000131

AB WO 200157036 A UPAB: 20011211

NOVELTY - New nicotinamide benzofused-heterocyclyl derivatives (I).

DETAILED DESCRIPTION - Nicotinamide benzofused-heterocyclyl derivatives of formula (I) and its salts are new:

m = 0-2;

n = 1 or 2;

W' = -O-, -S(=O)t- or -N(R3)-;

t = 0-2;

R3 = H, 1-3C alkyl, 1-3C alkoxy, OH, phenyl or benzyl;

R4 = (a) H, F, Cl, 2-4C alkynyl, R12, OR12, S(=O)pR12, -C(=O)OR12, OR(=O)R12, CN, NO2, substituted amines (substituted by R12, R14 and R15), (b) 1-4C alkyl or 1-4C alkoxy, all optionally substituted by 0-3 F or Cl or 0-1 of 1-2C alkoxycarbonyl, 1-2C alkylcarbonyl or 1-2C alkylcarbonyloxy or (c) aryl or heterocyclic);

R5, R6 taken together = a substituent of formula (ii)-(vi);

R7, R8 = H, CH3, OR14 or R14;

Z = OR12, C(=O)R12 or CN;

R14 = H, CH2 or CH2CH3;

R15 = H, C(=O)OR12, C(=O)NR12R13, 1-4C alkyl, 2-4C alkenyl, 1-2C alkoxy, 3-7C cycloalkyl or phenyl (alkyl, alkenyl, alkoxy, cycloalkyl and phenyl are substituted by 0-2 R21;

R21 = F, Cl, C(=O)OR23, OH, CN, C(=O)NR23R24, NR23R24, NR23C(=O)R24, NR23C(=O)OR24, NR23S(=O)pR24 or S(=O)pNR23R24, 1-4C alkyl including dimethyl or 1-4C alkoxy (alkyl and alkoxy are substituted by 0-3 F, Cl, 1-2C alkoxycarbonyl, 1-2C alkylcarbonyl or 1-2C alkylcarbonyloxy;

R23, R24 = H or 1-2C alkyl;

Y' = =C(RE)- or -(N-->(O))-;

RE = H, F, Cl, CN, NO2; 1-4C alkyl, 2-4C alkynyl, fluorinated 1-3C alkyl, 1-3C alkoxy, fluorinated 1-3C alkyloxy, OH or C(=O)NR12R13;

RA, RB = H, F, CF3, 1-6C alkyl, 3-7C cycloalkyl, phenyl, benzyl or a heterocyclic; and

R10 = F, Cl, CF3, CN, 1-2C alkyl, OR12, C(=O)OR12, -O-C(=O)R13, C(=O)NR12R13, O-C(=O)R13, -C(=O)NR12R13, -O-C(=O)NR12R13, NR12R13, NR12C(=O)R13, NR12C(=O)OR13, NR12S(=O)2R13 or S(=O)2NR12R12; and

R12, R13 = H, 1-4C alkyl, 2-4C alkynyl, 3-6C cycloalkyl, phenyl, benzyl or a monocyclic heterocyclic; or

RA and RB taken together = a spiro moiety of formula (i) (provided m = 1), which is substituted as to any one or more carbon atoms, by 0-3 substituents R10;

r, s = 0-4;

QA = -CH2-, -CHF, -CF2, NF2, -NR12-, -O- or -S(=O)-;

t = 0-2;

RC, RD = as for RA and RB, except that at least one of RC and RD must be H;

Q = heterocycle or aryl

R1, R2 = H, F, Cl, OR12, S(=O)pR12, -C(=O)OR12, OC(=O)R12, CN, NO2,

-C(=O)NR12R13, OC(=O)NR12R13, NR14C(=O)NR15R12, NR14C(=NR14)NR15R12, NR14C(=NCN)NR15R12, NR14C(=N-NO2)NR15R12, C(=NR14)NR15R12, OC(=NR14)NR15R12, OC(=N-NO2)NR15R12, NR15R12, CH2NR15R12, NR14C(=O)R12, NR14C(=O)OR12, NR14S(=O)pR13 or S(=O)pNR12R13; and
p = 0-2.

With the following proviso's:

(1) For all other meanings of RA or RB, when R10 as a substituted of RA or RB has the meaning OR12, -O-C(=)R13 or -OC(=O)NR12R13, the positional relationship of them, as a meaning of Z, is other than a vicinal one; and

(2) the sum of r = s is at least 1 but not greater than 5.

INDEPENDENT CLAIMS are also included for the following:

(1) pharmaceutical composition for use in treating a subject suffering from a disease, disorder or condition medicated by the PDE4 isozyme, whereby it regulates the activation and degranulation of eosinophils, comprising (I) with a carrier; and

(2) combination of (I) with other therapeutic compounds.

ACTIVITY - Antiasthmatic; bronchodilator; antiinflammatory; antibacterial; virucide; fungicide; opthalmological; antiallergic; antidote; protozoacide; antirheumatic; antiarthritic; analgesic; antigout; antipyretic; dermatological; antipsoriatic; neuroprotective; vasotropic; hepatotropic; antiulcer; cytostatic; antidiabetic; immunomodulator; nephrotropic; antidepressant; antiparkinsonian; anti-HIV; nootropic; hypotensive.

No appropriate biological data given.

MECHANISM OF ACTION - PDE Isozyme inhibitor; Leukotriene biosynthesis inhibitor; Leukotriene biosynthesis inhibitor; (5-LO) inhibitor; (FLAP) antagonist; isoform PDE4D inhibitor; dual inhibitor of (5-LO); (PAF) antagonist; antihistaminic H1 receptor antagonist; gastroprotective H2 receptor antagonist; alpha 1-and alpha 2-adrenorecptor agonist vasoconstrictor; beta 1- beta 4-adrenoreceptor agonist; Muscarinic receptor antagonist; COX-1 inhibitor (NSAIDs); COX-2 selective inhibitor; (IGF-1) mimetic; (PAF) antagonist; Anti-tumor necrosis factor (TNF alpha); (ICE) inhibitor; IMPDH inhibitor; VLA-4 antagonist; MAP kinase inhibitor; Glucose-6-phosphate dehydrogenase inhibitor; Kinin-B1- and B2-receptor antagonist; Xanthine oxidase inhibitor; matrix metalloprotease inhibitor.

USE - (I) is useful for treating asthma, including infective asthma caused by bacterial, fungal, protozoal or viral infection, bronchoconstriction, chronic bronchitis, small airways obstruction, emphysema, obstructive or inflammatory airways diseases from pneumoconiosis, chronic eosinophilic pneumonia, chronic obstructive pulmonary diseases such as chronic bronchitis, pulmonary emphysema or dyspnea, pneumoconiosis, etiology or pathogenesis or pneumoconiosis from aluminosis or bauxite worker's disease, anthracosis or minor's asthma, ptilosis, siderosis, silicosis or grinders disease, byssinosis or cotton-dust asthma and talc pneumoconiosis, bronchiectasis, seasonal allergic rhinitis, rheumatoid arthritis, gout and fever and pain, eosinophil-related disorder, dermatitis or eczema, urticaria, conjunctivitis, uveitis, psoriasis, multiple sclerosis, autoimmune/ inflammatory diseases including hemolytic anemia, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, polychondritis, scleroderma, Wegner's granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Stevens-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, endocrin opthamopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumontis, primary bilary cirrhois, diabetes, lung fibrosis, glomerulonephritis, hyperproliferative skin diseases,

psoriasis, dermatitis, benign famillal pemhigus, pemphigus erythematosus, pemphigus foliaceus, pemphigus vulgaris, prevention of allergenic graft rejection following organ transplantation, inflammatory bowel disease, septic shock, renal failure, cachexia and Addison's disease, cachexia, liver injury, pulmonary hypertension, osteoporosis, central nervous system disorders e.g. depression, Parkinson's disease, learning and memory impairment, tardive dyskinesia, drug dependence, arteriosclerotic dementia and other dementias, infection, especially infection by viruses such as viruses that increase the production of TNF- alpha in their host such as HIV-1, HIV-2 and HIV-3, cytomegalovirus, CMV, influenza, adenoviruses, herpes viruses, yeast and fungus infections (all claimed uses).
Dwg.0/0

L92 ANSWER 53 OF 53 WPIX (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-565224 [63] WPIX
DOC. NO. CPI: C2001-167720
TITLE: New pyrimidine carboxamides are PDE4 isozyme inhibitors useful for treating diseases, disorders or conditions e.g. asthma and bronchitis, mediated by the PDE4 isozyme in which it regulates the activation and degranulation of eosinophils.
DERWENT CLASS: B03
INVENTOR(S): CHAMBERS, R J; MAGEE, T V; MARFAT, A
PATENT ASSIGNEE(S): (PFIZ) PFIZER PROD INC
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001057025	A1	20010809	(200163)*	EN	162
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001027003	A	20010814	(200173)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001057025	A1	WO 2001-IB125	20010130
AU 2001027003	A	AU 2001-27003	20010130

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001027003	A Based on	WO 200157025

PRIORITY APPLN. INFO: US 2000-179282P 20000131
AB WO 200157025 A UPAB: 20020508
NOVELTY - Pyrimidine carboxamides (I) and their salts are new.
DETAILED DESCRIPTION - Pyrimidine carboxamides of formula (I) and their salts are new.
j, k, m = 0-1;
n = 1-2;

W = -O-, -S(=O)t- or -N(R3)-;
t = 0-2;
R3 = H, 1-3C alkyl or OR12;
RA, RB = H, F or CF3 or 1-4C alkyl, 3-7C cycloalkyl or benzyl (each optionally substituted); or
when m = 1, RA+RB = spiro moiety of formula (i);
R10 = F, Cl, CF3, CN, OR12, 1-2C alkyl, hydroxy 1-2C alkyl, O-C(=O)R13, O-C(=O)NR12R13, NR12R13, NR12C(=O)R13, NR12C(=O)OR13, -NR12S(=O)2R13 or -S(=O)2NR12R13;
R12, R13 = H; 1-4C alkyl or benzyl (both optionally substituted);
r, s = 0-4;
QA = CH2, CHF, CF2, -N(R3), O or S(=O)t;
RC, RD = RA;
ZA = (un)saturated cyclic or bicyclic 3-9C heterocyclic, 3-7C cycloalkyl, phenyl or pyridyl (each optionally substituted);
R9 = H or 1-4C alkyl;
R16 = F, Cl, CN, OR12, 1-4C alkyl, 3-7C cycloalkyl, CF3, C(=O)OR12, NO2, NR12R13, 1-4C alkylamino, phenyl or benzyl (each alkyl, alkoxy or cycloalkyl being optionally substituted);
R18 = F, Cl, CN, OR12, CF3, NR12R13 or phenyl;
R4 = F, Cl, CN, OR12 , S(=O)pR12, C(=O)OR12, OC(=O)R12, NO2, C(=O)NR12R13, OC(=O)NR12R13, NR12R13, NR14C(=O)R12, NR14C(=O)OR12, NR14S(=O)pR12 or S(=O)pNR12R13; or 1-4C alkyl or 1-4C alkoxy (each optionally substituted) or benzyl or heterocyclyl (each optionally substituted) or when ZA = phenyl, R4 on adjacent C atoms together with the C atoms to which they are attached and the phenyl ring form benzofused heterocyclyl;
p = 0-2;
R14 = H, CH3 or CH2CH3;
ZB = cyclohexyl, cyclopentenyl, cyclohexenyl, norbornanyl, norbornenyl, bicyclo(2.2.2)octanyl, bycyclo(3.2.1)octanyl, bicyclo(3.3.0)octanyl, bicyclo(2.2.2)oct-5-enyl, bicyclo(2.2.2)oct-7-enyl, bicyclo(3.3.1)nonanyl or adamantanyl;
R1, R2 = H, F, Cl, OR12, -S(=O)pR12, -C(=O)OR12, -OC(=O)R12, CN, NO2, C(=O)NR12R13, NR12R13 or S(=O)pNR12R13;
E = H, F, Cl, CN, OR12, 1-4C alkyl, hydroxy 1-4C alkyl, CF3, NO2, NR12R13, NR12S(=O)2R13 or S(=O)2NR12R13 provided that when R10 = OR12, OC(=O)R12 or OC(=O)NR12R13 and E = OR12, the positional relationship is not vicinal;
R7, R8 = H, F, Cl, OR12, 1-4C alkyl, hydroxy 1-4C alkyl, CF3, C(=O)OR12, NR12R13 or hydroxy 1-4C alkylamino or phenyl, benzyl or heterocyclyl (each optionally substituted); and
with provisos.

NB: Definitions for R5 and R6 are not given.

The full definitions are given in the DEFINITIONS (Full Definitions) Field.

AN INDEPENDENT CLAIM is also included for a combination of (I) with one or more compounds (VIII) selected from e.g. **leukotriene** biosynthesis inhibitors and receptor antagonists for leucotrienes.

ACTIVITY - Antiinflammatory; Antiallergic; Antirheumatic; Antiarthritic; Antipyretic; Antigout; Antiasthmatic; Dermatological; Cardiovascular-Gen; Respiratory-Gen; Ophthalmological; Antipsoriatic; Antipruritic; Neuroprotective; Immunosuppressive; Antibacterial; Hepatoropic; Hypotensive; Osteopathic; Virucide; Anti-HIV; Cytostatic; Nephrotropic; Antiulcer; Antidiabetic; Vulnerary.

MECHANISM OF ACTION - PDE4 isozyme inhibitor.

USE - For treating diseases, disorders or conditions mediated by the PDE4 isozyme in which it regulates the activation and degranulation of

eosinophils. The disease, disorder or condition is one or more of asthma, etiology or pathogenesis; chronic or acute bronchoconstriction, chronic bronchitis, small airways obstruction, emphysema, obstructive or inflammatory airways diseases, etiology or pathogenesis; pneumonconiosis , etiology or pathogenesis; seasonal allergic rhinitis, perennial allergic rhinitis, sinusitis, etiology or pathogenesis; rheumatoid arthritis, etiology or pathogenesis; gout and fever and pain associated with inflammation, eosinophil-related disorders, etiology or pathogenesis; atopic dermatitis or allergic dermatitis or allergic or atopic eczema), urticaria of any type, etiology or pathogenesis; conjunctivitis, etiology or pathogenesis; uveitis, etiology or pathogenesis; psoriasis, multiple sclerosis, etiology or pathogenesis; autoimmune diseases, etiology or pathogenesis; prevention of allogeneic graft rejection following organ transplantation, inflammatory bowel disease, etiology or pathogenesis; septic shock, etiology or pathogenesis; liver injury, pulmonary hypertension and hypoxia-induced pulmonary hypertension, bone loss diseases, primary osteoporosis and secondary osteoporosis, central nervous system disorders, etiology or pathogenesis; infection (especially infection by viruses which increase the production of TNF alpha in their host or which are sensitive to upregulation of TNF- alpha in their host so that their replication or other vital activities are adversely impacted, including a virus selected from HIV-1, HIV-2 and HIV-3, cytomegalovirus, CMV, influenza, adenoviruses and Herpes viruses including Herpes zoster and Herpes simplex), yeast and fungus infections in which the yeast and fungi are sensitive to upregulation by TNF- alpha or elicit TNF- alpha production in their host when administered in conjunction with other drugs for the treatment of systemic yeast and fungus infections (including polymixins, Polymycin B, imidazoles, clotrimazole, econazole, miconazole and ketoconazole, triazoles, fluconazole and itranazole and amphotericins, Amphotericin B and liposomal Amphotericin B) and ischemia-reperfusion injury, autoimmune diabetes, retinal autoimmunity, chronic lymphocytic leukemia, HIV infections, lupus erythematosus, kidney and ureter disease, urogenital and gastrointestinal disorders and prostated inflammatory diseases and conditions, respiratory diseases and conditions , infectious diseases and conditions, immune diseases and conditions and other diseases and conditions (comprising bone resorption diseases, reperfusion injury, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), HIV infection or AIDS related complex, keloid formation, scar tissue formation, type 1 diabetes mellitus and leukemia.

(I) may be administered alone or in combination with e.g. one or more leukotriene biosynthesis inhibitors , PDE4 inhibitors and tryptase inhibitors.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	73.10	482.04

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-8.05	-8.05

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 12:35:39 ON 06 NOV 2002